ISSN 0003-2999
Volume 67, Number 9, September 1988

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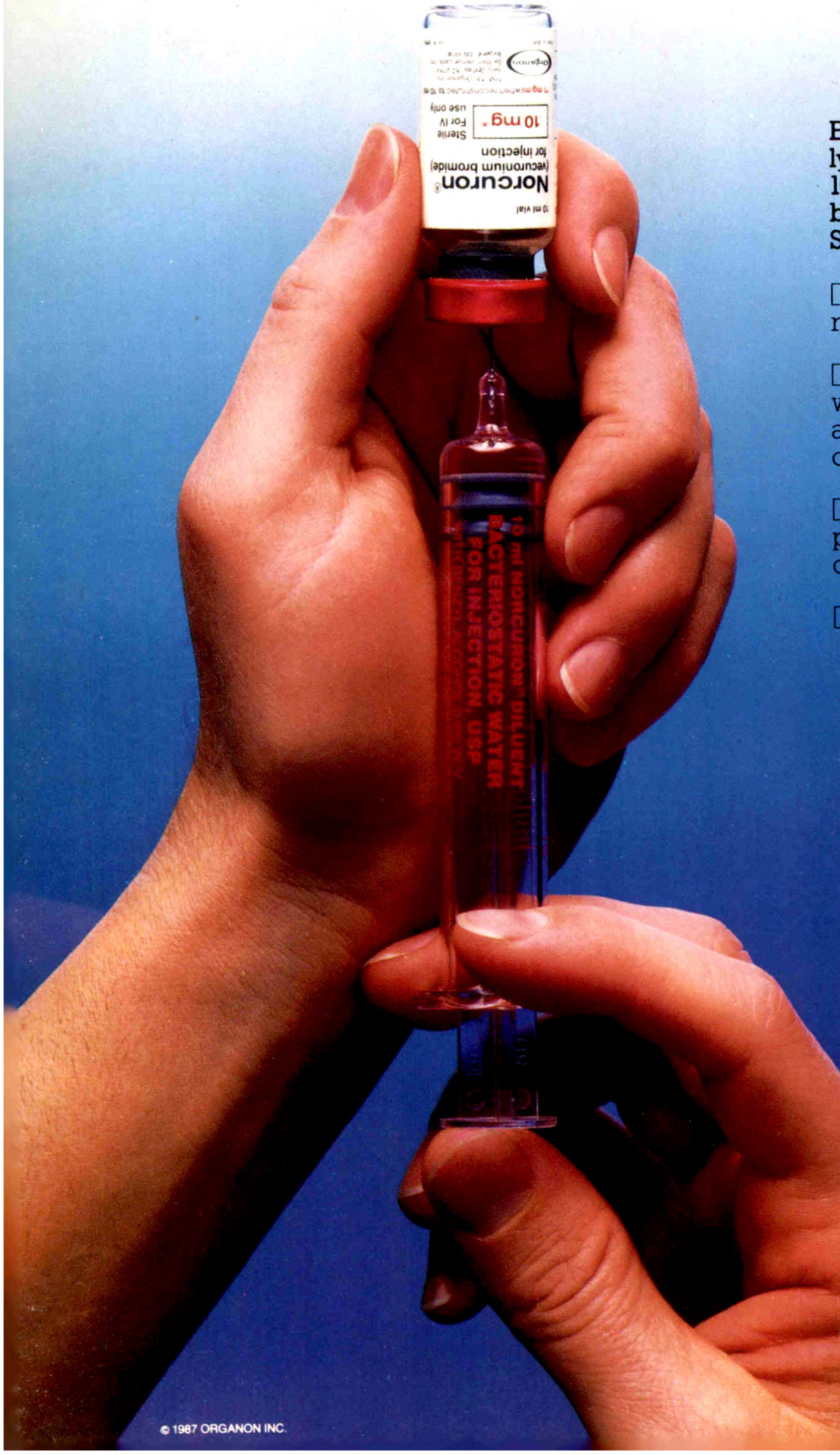

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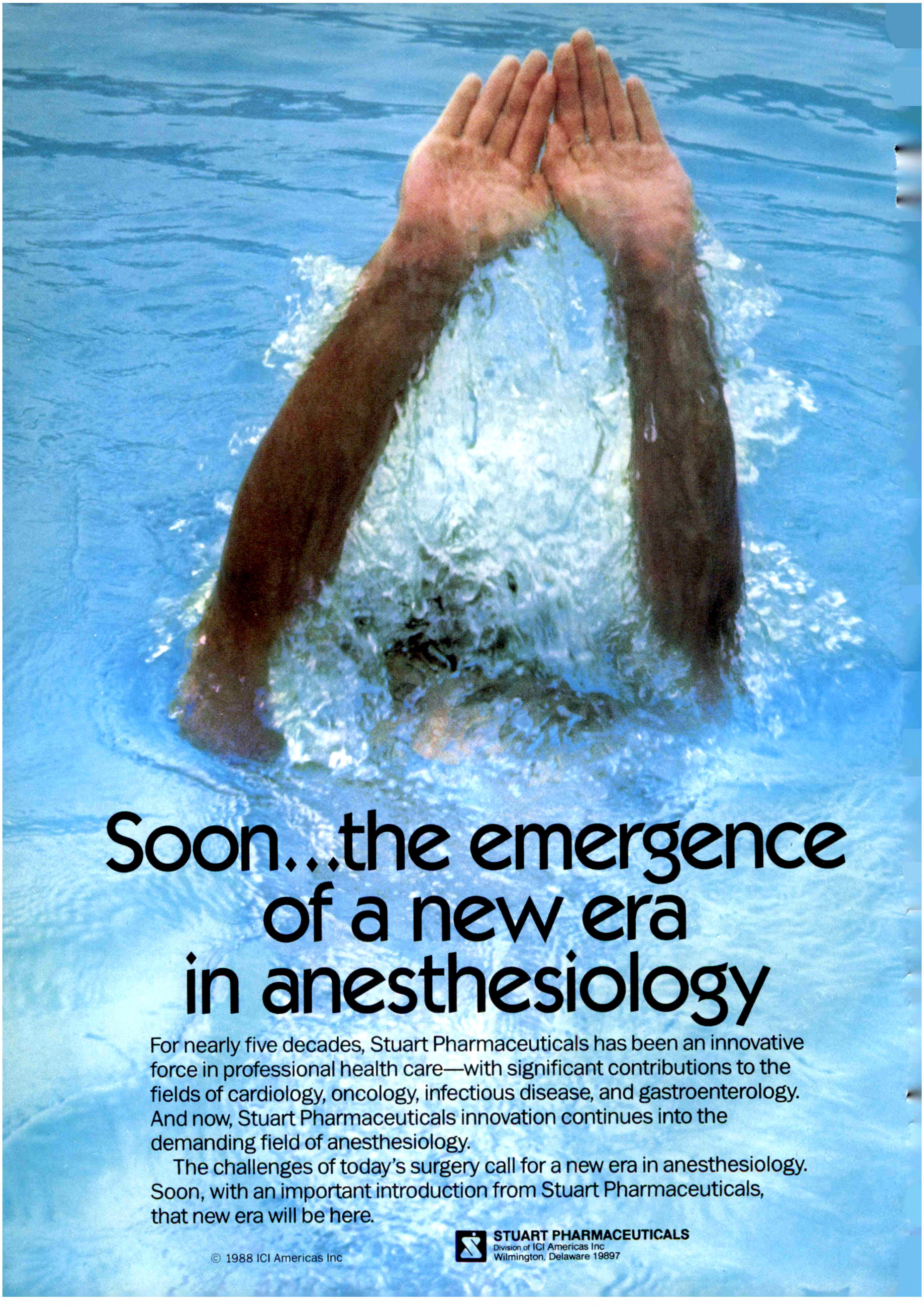

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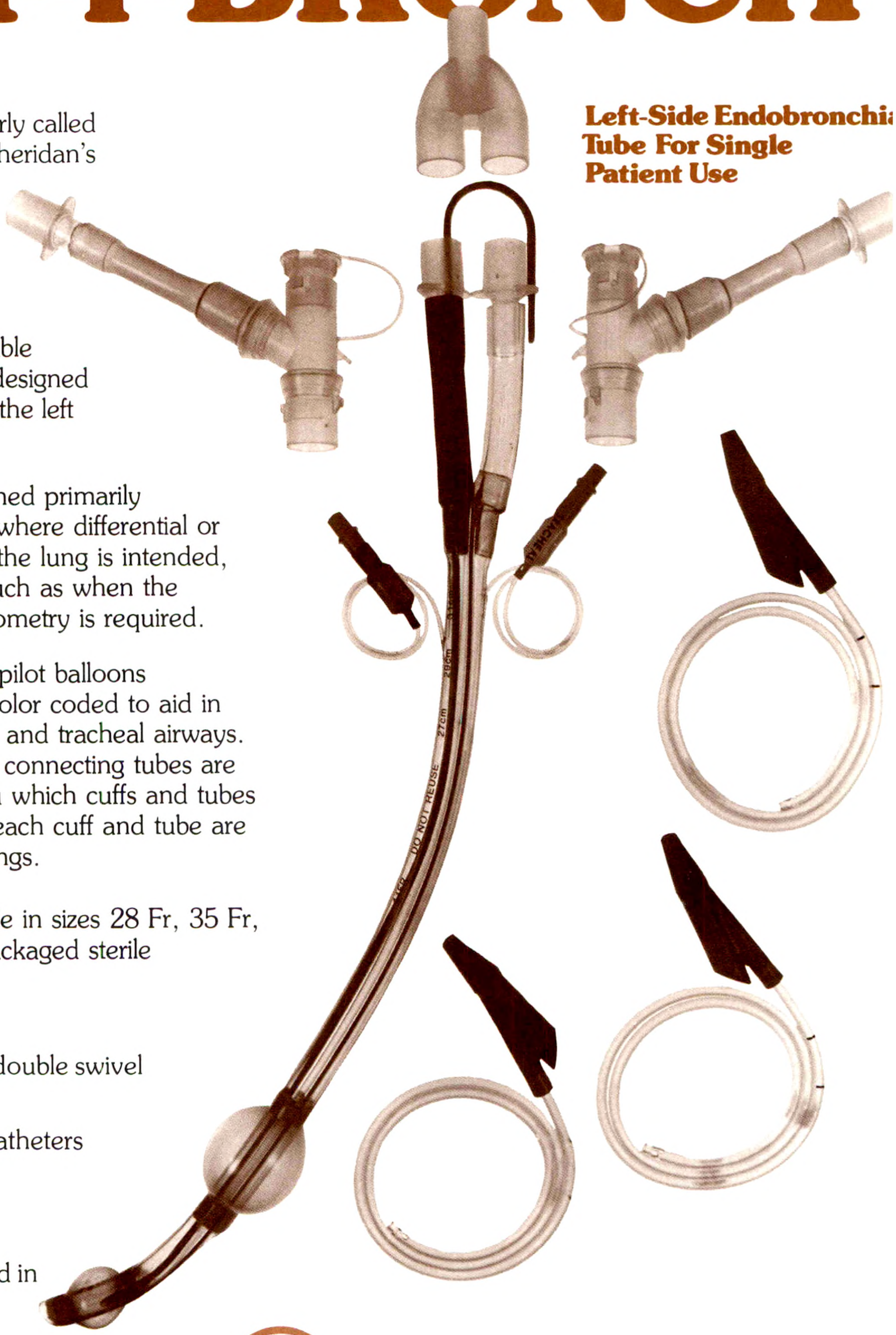

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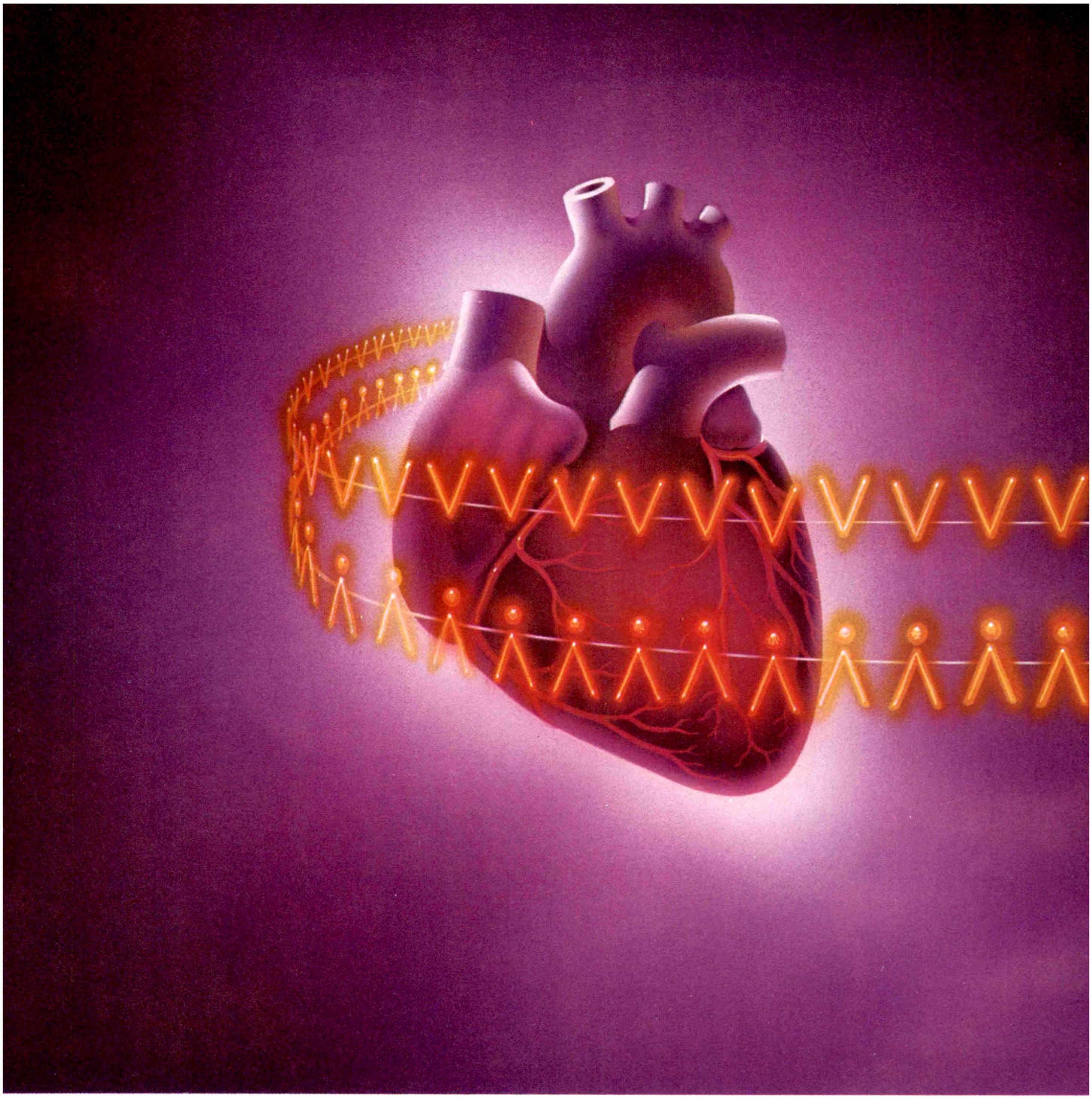

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Epidural Blood Flow and Regression of Sensory Analgesia during Continuous Postoperative Epidural Infusion of Bupivacaine

Torben Mogensen, MD, Liselotte Højgaard, MD, Nicholas B. Scott, FRCS (ED), Jens H. Henriksen, MD, PhD, and Henrik Kehlet, MD, PhD

MOGENSEN T, HØJGAARD L, SCOTT NB, HENRIKSEN JH, KEHLET H. Epidural blood flow and regression of sensory analgesia during continuous postoperative epidural infusion of bupivacaine. Anesth Analg 1988;67: 809–13.

Epidural blood flow was measured in seven patients undergoing elective abdominal surgery during combined lumbar epidural and general anesthesia. After an initial dose of 20 ml plain bupivacaine 0.5%, a continuous epidural infusion of bupivacaine 0.5% (8 ml/hr) was given for 16 hours for postoperative pain relief. The epidural blood flow was measured by a local ^{133}Xe clearance technique in which 15–35 MBq ^{133}Xe diluted in 1 ml saline was injected through the epidural catheter on the day before surgery (no bupivacaine), 30 minutes after the initial dose of bupivacaine on the morning before surgery, and 8, 12, and 16 hours later during the continuous infusion. Initial blood flow was 6.0 ± 0.7 ml/min per 100 g tissue (mean ± SEM). After epidural bupivacaine, blood flow increased in all seven patients to 7.4 ± 0.7 ml ($P < 0.02$). Initial level of sensory analgesia was T4.5 ± 0.17 (mean ± SEM). Postoperatively, two patients maintained the initial level of sensory analgesia and low pain score throughout the 16-hour study. In these two patients epidural blood flow remained constant after the initial increase. Flow increased further to 10.3 ± 0.8 ml/min per 100 g tissue ($P < 0.03$) in the other five patients as the level of sensory analgesia regressed postoperatively. These data suggest that changes in epidural blood flow during continuous epidural infusion of bupivacaine, and thus changes in rates of vascular absorption of bupivacaine from the epidural space, may be an important factor contributing to differences in rates of regression of sensory analgesia.

Key Words: ANESTHETIC TECHNIQUES—epidural. ANATOMY, EPIDURAL SPACE—blood flow.

Epidural neural blockade with local anesthetics is useful in the alleviation of postoperative pain, but maintenance of level of sensory analgesia may be difficult because of regression of sensory analgesia (1–5) as well as anatomic factors within the epidural space and changes in position of the epidural catheter (6,7).

The pathogenesis of regression of sensory analgesia remains controversial (7,8) but involves either a true reduction in effect at the receptor level or a decrease in the fraction of drug reaching the receptor. An increased clearance of the local anesthetic as an explanation for decreases in efficacy of epidural bupivacaine for relief of postoperative pain due to a increase in epidural blood flow has been suggeste (7), but no data have been published.

The purpose of this study was to investigate th relation between changes in epidural blood flo assessed by a xenon clearance technique and change in sensory level of analgesia during continuous ep dural infusion of bupivacaine in patients after abdominal surgery.

Methods

Patients, Anesthesia, and Analgesia

Seven patients, mean age 56 years (range 32–82 height 171 cm (155–184), body weight 64 kg (55–76 male/female ratio 3/4, scheduled for combined ep dural and general anesthesia during major abdomin surgery, were studied. General anesthesia was ir duced with thiopental (3–5 mg/kg), preceded b precurarization with pancuronium (0.01 mg/kg) an

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Received from the departments of Anesthesiology, Clinical Physiology/Nuclear Medicine, and Surgical Gastroenterology, Hvidovre University Hospital, University of Copenhagen, Copenhagen, Denmark. Accepted for publication May 2, 1988.

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This work was supported by a grant from Astra Alab, Södertälje, Sweden.

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followed by succinylcholine (1.5 mg/kg) to facilitate orotracheal intubation. Anesthesia was maintained with N_2O/O_2 (2:1) and halothane (0.25–1.0%).

The surgical procedures included small bowel resection (two) and upper abdominal exploratory laparotomy, right hemicolectomy, cholecystectomy, pancreatico-gastrostomy, and gastric antrectomy (one each). The study was approved by our Ethics Committee for Medical Research. Informed consent was obtained from each patient, and no complications or side effects were seen.

The epidural catheter used in this study was inserted between L2 and L3 on the day before surgery. The epidural blood flow was then measured by epidural injection of ^{133}Xe diluted in isotonic saline (see later). Immediately after the injection, isotonic saline was delivered by an infusion pump at a rate of 8 ml/hr during the measurement. One hour before surgery, 20 ml plain bupivacaine 0.5% was given, and a continuous infusion of bupivacaine 0.5% 8 ml/hr was started and scheduled to continue for 16 hours. Epidural blood flow was again measured by repeated ^{133}Xe injections 30 minutes and 8, 12, and 16 hours after the initial dose of bupivacaine. Radiation dose to the epidural space was approximately 1 mSv.

Pain scores on a five-point scale (no pain, slight pain, moderate pain, severe pain, and unbearable pain) and level of sensory analgesia (pinprick) were determined hourly by one of the authors (TM) without knowing the result of blood flow measurements. If the pain score reached 2 or more, the patients were treated by epidural (4 mg) and IV morphine (4–6 mg) together with the bupivacaine infusion.

When changes in epidural blood flow and changes in pain score were compared, only the observations made before surgery and at the first appearance of pain and regression of sensory analgesia were used. The same method was used for comparison of changes in epidural blood flow and changes in sensory level.

Epidural Blood Flow Determination

Blood flow in the epidural space was measured by a local ^{133}Xe clearance technique according to the principles followed in measurements of cutaneous and subcutaneous blood flows (9). In this study, 15–35 MBq [the becquerel [Bq] is the new SI unit replacing the curie; 1 mCi = 37 MBq] ^{133}Xe diluted in 1 ml sterile isotonic saline was injected through the epidural catheter, followed by irrigation of the catheter with 3 ml sterile isotonic saline.

The gamma emissions were measured externally using a gamma camera (General Electric Maxi Camera 400 zs) with a 40-cm field of view and low-energy collimator. The posterior recordings over the back were stored in a PDP 11 digital computer, using 30-second frames, for 30 minutes. The epidural area with isotope present was outlined, and the curve describing ^{133}Xe clearance was constituted (Fig. 1).

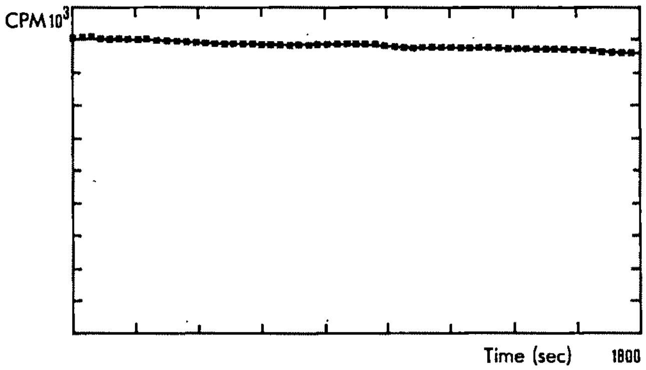

Figure 1. A xenon-133 washout curve.

The rate constant of disappearance (K, $\min^{-1}$) was determined from the regression line using a modified least squares method for the logarithmically transformed count rates versus time. The epidural blood flow perfusion coefficient (= epidural blood flow per 100 g tissue) (EBF) was determined by the equation

$$\text{EBF} = \lambda K \cdot 100 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g tissue})^{-1},$$

where λ is the tissue-blood partition coefficient of xenon. A value equal to that of adipose tissue, 5.0 ml/g tissue, was used. Although histologic examinations have revealed that the tissue in the epidural space has a composition comparable to that of subcutaneous tissue (10), chemical examination of epidural tissue suggests a λ value of 5 ml/g tissue to be appropriate (unpublished observations). Although we have used the same value for λ in all patients, it must be emphasized that λ depends on the amount of lipid and therefore might differ from one patient to another. However, this does not influence the validity of measurements of changes in the epidural blood flow in individual patients.

During the measurements of epidural blood flow, complete dispersion of ^{133}Xe in the epidural space could be seen by the gamma camera, and there was no sign of radial diffusion. In an initial experiment there was no evidence of change in the disappearance rate of ^{133}Xe associated with increasing the volume in the epidural space by injecting 20 ml saline, indicating that the partition coefficient remained constant and independent of fluid volume in the epidural space. The ^{133}Xe washout curve was monoexponential during each period of measurement (30 minutes).

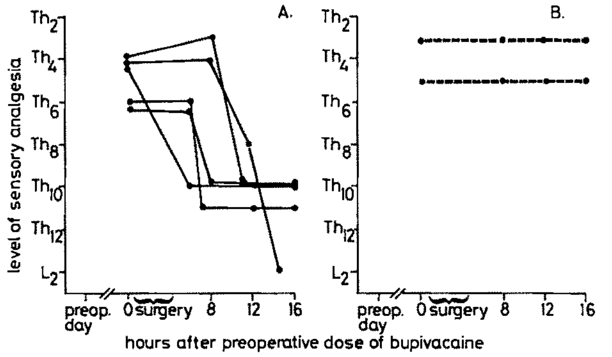

Figure 2. Level of sensory analgesia during postoperative epidural infusion of bupivacaine 0.5% 8 ml/hr in patients (A) with and (B) without regression of sensory analgesia.

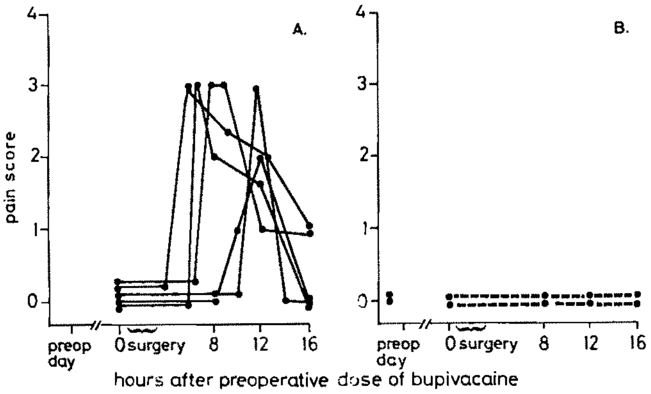

Figure 3. Pain scores during postoperative epidural infusion of bupivacaine 0.5% 8 ml/hr in patients (A) with and (B) without regression of sensory analgesia.

Results are expressed as mean ± SEM. Data were analyzed using Wilcoxon's test for paired data, the Mann-Whitney test for unpaired data comparing two groups, and Friedman's analysis of variance. $P < 0.05$ was considered significant.

Results

Changes in sensory levels of analgesia and pain scores are illustrated in Figures 2 and 3. In five of the seven patients the level of sensory analgesia decreased more than five segments below the initial level, with a resulting increase in pain score. Thus, at 16 hours only two patients remained pain-free with a stable level of sensory analgesia without morphine administration.

Epidural blood flow increased significantly in all seven patients after induction of epidural analgesia from an initial level of 6.0 ± 0.7 ml/min per 100 g tissue to 7.4 ± 0.7 ml/min per 100 g tissue. In the two patients with stable levels of sensory analgesia, no further increase in the epidural blood flow was observed during the study period. Two of the other five patients had stable levels of sensory analgesia and an almost constant epidural blood flow at 8 hours, but 12 hours after the initial dose of bupivacaine the level of sensory analgesia had decreased with an accompanying increase in epidural blood flow. In the remaining three patients, the level of analgesia decreased and epidural blood flow increased after 8 hours, with a further increase in epidural blood flow at 12 and 16 hours in two patients (Fig. 4).

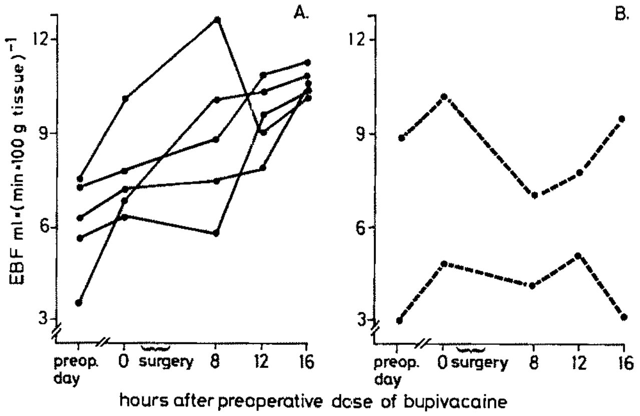

Figure 4. Epidural blood flow before and during continuous epidural infusion of bupivacaine 0.5% 8 ml/hr, before and after major abdominal surgery in patients (A) with and (B) without regression of sensory level of analgesia.

The relation between changes in epidural blood flow and change in level of sensory analgesia before and at the first assessment after additional morphine was given is seen in Figure 5A. Epidural blood flow in periods with stable levels of analgesia decreased 3 ± 6% below the value observed after the initial dose of bupivacaine. In the five patients in whom the level of analgesia decreased, the epidural blood flow increased 36 ± 7% (mean ± SEM) at the first measurement after the regression of sensory analgesia. The changes in epidural blood flow when the levels of sensory analgesia remained stable and when they regressed were significantly different. The same relation was seen between changes in epidural blood flow and changes in pain score (Fig. 5B).

The spread of the ^{133}Xe rostrally and caudally away from the site of injection into the epidural space averaged 13 ± 1, 15 = 2, 15 ± 2, 15 ± 3, 16 ± 2 cm (mean ±SEM) at the times they were measured ($P > 0.5$). There was no difference between the spread in patients with a stable level of analgesia and that in patients with regression of the level of analgesia.

Discussion

The nature of decay of sensory levels of analgesia during continuous or intermittent epidural injections

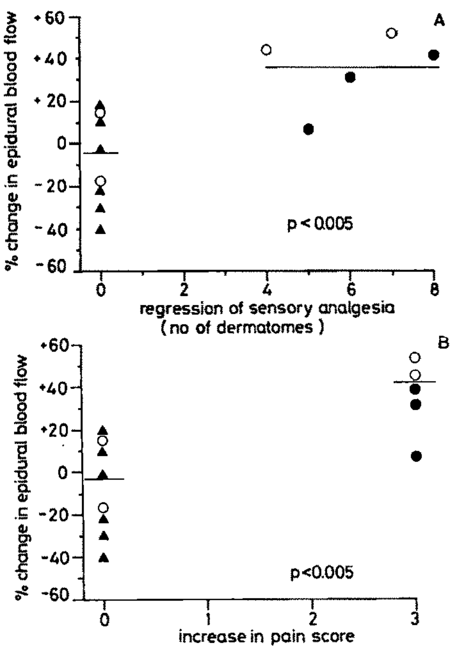

Figure 5. Relation between changes in epidural blood flow and (A) decreases in levels of sensory analgesia and (B) increases in pain score during postoperative epidural infusions of bupivacaine 0.5% 8 ml/hr. Values after the preoperative epidural bupivacaine administration were compared with postoperative values before regression of sensory analgesia and the first assessment after regression of sensory analgesia. $n = 13$, (▲) Two patients with three assessments during stable analgesia; (○) two patients with two assessments (one observation during stable analgesia and one after regression of analgesia); (●) three patients with one assessment (observations made after the rapid regression of analgesia).

of local anesthetics (1–5) has not been found to be influenced by patient characteristics such as height, body weight, serum albumin, or duration and site of surgery (11). The explanation for regression of analgesia remains unknown (7,8), but several hypotheses have been proposed, including increased systemic uptake of the local anesthetic at the injection site due to an increase in epidural blood flow.

The xenon clearance technique used in this study is a known method for flow measurement in various types of tissue, e.g., subcutaneous tissue. The method is accurate, sensitive, and reproducible (9). The linearity of the clearance curve found in this study (Fig. 1) is of the same quality as that of subcutaneous washout curves (9).

Our study, has demonstrated for the first time, with measurement of epidural blood flow, that epidural administration of bupivacaine 0.5% increases epidural blood flow. Skagen et al. (12) have shown that epidural blockade produced a 43% increase in subcutaneous blood flow in the leg. This indirect effect of local anesthetics is well-known: The sympathetic denervation causes peripheral vessels to dilate. When analyzing the vascular effects of epidural blockade on the epidural vessels, the direct effect of the local anesthetic must also be taken in account. Although most local anesthetics are generally regarded as vasodilators at the site of injection, they may produce systemic effects characterized by increased peripheral resistance (13).

However, Jorfeldt et al. (14) found a decrease in vascular resistance in the forearm, indicating a decrease in the tone of resistance vessels after intravenous administration of mepivacaine. When the sympathetic innervation was blocked before the mepivacaine was infused intravenously, there was no further decrease in vascular resistance below the level seen after the sympathetic blockade (14). Johns et al. (15) also reported that bupivacaine in low concentrations (0.0001–0.01%) produced vasoconstriction, while bupivacaine 0.1% and 0.25% did not alter arteriolar diameters significantly, although there was a tendency for vasodilatation (15). Epidural blood flow may therefore increase because of the sympathetic blockade produced by epidural bupivacaine, but this may also be due to direct effects of bupivacaine on epidural vessels. Whether the increases in epidural blood flows seen in this study are caused by an increasing afferent neural input from the periphery during the postoperative period or whether epidural blood flow usually rises postoperatively as a result of a postoperative increase in cardiac output cannot be answered, because we had no simultaneous measurements of cardiac output.

Mather et al. (16) have demonstrated an increase in plasma lidocaine concentrations when cardiac output was elevated by ephedrine during epidural analgesia in two patients. This may suggest that an increase in blood flow leads to increased systemic uptake of local anesthetics. However, prophylactic ephedrine did not influence duration of analgesia after epidural administration of bupivacaine in another study of 27 patients (17).

During the postoperative period we found a further increase in epidural blood flow in the five patients who had a pronounced decay in sensory level of analgesia and increase in pain score, but not in the two patients with stable levels of analgesia.

Pain itself seems to have little effect on epidural blood flow, as there was no change in the epidural blood flow when the patients in pain were given either epidural or systemic morphine in amounts adequate to relieve pain. However, whatever the mechanism of changes in epidural blood flow may be during postoperative continuous epidural bupivacaine administration, this change in epidural blood flow may be an important contributing factor to regression of analgesia.

In a previous study we demonstrated that surgical injury may enhance the regression of sensory analgesia because a more stable blockade was seen in patients with chronic nonsurgical pain than in postoperative patients (18). However, whether this finding represents differences in epidural blood flow or a postoperative increase in excitability in peripheral nociceptors and the spinal cord (19,20) with assumed subsequent competitive increase in afferent input is unknown. We also previously demonstrated that both systemic and epidural morphine can counteract the regression in sensory analgesia in postoperative patients (21,22). The reason for this is unknown, but perhaps it is due to an inhibitory effect of morphine on afferent traffic that thereby hinders breakthrough of afferent stimuli at the most rostrad (and weakest) part of the epidural blockade. In the present study there was no increase in sensory level of analgesia after treatment with morphine, probably because the dose of IV morphine was small (5 mg) and epidural morphine was given after the decay of sensory analgesia. In four of the five patients the decay stopped at the T12 level.

In conclusion, our results show that epidural blockade with bupivacaine 0.5% increases epidural blood flow, with a further increase in epidural blood flow in patients in whom regression of sensory analgesia developed during continuous postoperative epidural infusion of bupivacaine. In contrast, patients with a stable level of sensory analgesia showed no further increase in epidural blood flow. These results suggest that an increase in epidural blood flow, with assumed increased clearance of bupivacaine from the epidural space, is an important factor leading to regression of analgesia during continuous epidural bupivacaine administration.

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Gradual or Abrupt Nitrous Oxide Administration in a Canine Model of Critical Coronary Stenosis Induces Regional Myocardial Dysfunction That Is Worsened by Halothane

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LEONE BJ, PHILBIN DM, LEHOT J-J, FOËX P, RYDER WA. Gradual or abrupt nitrous oxide administration in a canine model of critical coronary stenosis induces regional myocardial dysfunction that is worsened by halothane. Anesth Analg 1988;67:814–22.

The existence of a dose–response relation between nitrous oxide concentration and regional dysfunction in compromised myocardium, and whether or not halothane-induced myocardial depression alleviated this regional dysfunction was examined. Nitrous oxide was administered to eight dogs with experimentally induced left anterior descending coronary artery (LAD) critical stenosis during fentanyl (100 μg/kg bolus plus 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) anesthesia. Two modes of nitrous oxide administration were employed: gradual (in steps of 20% inspired, i.e., 0%, 20%, 40%, and 60% inspired) and abrupt (0–60% inspired). Regional myocardial function was assessed by sonomicrometry. Regional dysfunction in the compromised myocardium, in the form of postsystolic shortening (PSS), increased above baseline levels during 40% (4.2 ± 2.3% to 12.1 ± 3.9%, $P < 0.05$) and 60% (4.2 ± 2.3% to 12.5 ± 3.6%, $P < 0.05$) inspired nitrous oxide (gradual administration) and also during abrupt 60% nitrous oxide administration (6.4 ± 2.6% to 9.9 ± 3.2%, $P < 0.05$). After abrupt 60% inspired nitrous oxide administration, halothane (0.7% inspired) was introduced and caused decreases in mean arterial pressure (106.1 ± 4.5 mm Hg to 76.2 ± 5.5 mm Hg, $P < 0.05$) and peak LV dP/dt (1700 ± 150 mm Hg/sec to 1100 ± 100 mm Hg/sec, $P < 0.05$). Halothane caused a marked increase in PSS (9.9 ± 3.2% to 30.8 ± 12.6%, $P < 0.05$). Thus nitrous oxide administration caused regional dysfunction in myocardium supplied by a critically narrowed LAD whether administered gradually or abruptly and at concentrations as low as 40% inspired. The addition of halothane to decrease myocardial oxygen demand resulted in marked worsening, rather than alleviation, of regional myocardial dysfunction.

Key Words: ANESTHETICS, VOLATILE—halothane. ANESTHETICS, GASES—nitrous oxide. HEART, CORONARY ARTERY DISEASE—myocardial ischemia; ventricular function.

Regional myocardial function is considered a sensitive indicator of regional ischemia in areas of limited coronary flow (1). Regional dysfunction, seen as continued myocardial shortening after systole, is a consistent feature of regional ischemia in compromised myocardium (2,3). The degree of dysfunction produced by volatile anesthetics may be related to their hemodynamic effects (4), their effects on coronary hemodynamics in regions of compromised myocardial blood flow (2), or some as yet undefined intrinsic effect of volatile anesthetics. In contrast, increased doses of synthetic narcotics have no deleterious effects on regional function and do not increase regional dysfunction (5).

Nitrous oxide (N_2O) is widely used in patients with severe coronary artery disease. However, our previous studies have shown that regional dysfunction in compromised myocardium, in the form of postsystolic shortening, occurs with the abrupt introduction of nitrous oxide (5). Similarly, the introduction of nitrous oxide with halothane-based anesthesia caused regional dysfunction in compromised myocardium (6). The present study was designed to compare

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Supported in part by grants G8002204SA and G8306850SA from the Medical Research Council. Dr. Lehot was the recipient of a MRC/INSERM Fellowship.

Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1987, Atlanta, Georgia.

Received from the Nuffield Department of Anaesthetics, University of Oxford, Radcliffe Infirmary, Oxford, U.K. Accepted for publication February 23, 1988.

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the effect of nitrous oxide given in a stepwise fashion, measuring any dose-related changes in regional function, with the effect of a "bolus" of nitrous oxide similar to our previous studies (5,6). Subsequent to the bolus introduction of nitrous oxide, halothane was given, and its effects on the regional function of the compromised myocardium were observed.

Methods

The methods employed in this study conform to the Animals (Scientific Procedures) Act of 1986 (U.K.). Eight mongrel dogs (weighing 17–22 kg) were premedicated with IM morphine sulfate (0.1 mg/kg), and anesthesia was induced with intravenous thiopental (7 mg/kg). The trachea was intubated, and intermittent positive-pressure ventilation was begun with 40% oxygen in nitrogen at a rate of 12 breaths/min with a tidal volume of 30 ml/kg with the dog in a right lateral decubitus position. Carbon dioxide concentration (end-tidal) was measured by infrared analysis, and tidal volume and fresh-gas flow of the nonrebreathing system were adjusted to maintain carbon dioxide between 4.5 and 5.5%. Esophageal temperature was measured continuously and maintained between 37 and 38°C with a heating element incorporated into the operating table. During the surgical preparation, anesthesia was maintained with halothane (1.2–1.5% inspired).

An intravenous cannula was placed in the inferior vena cava via the femoral vein. A constant infusion of balanced salt solution (4 $ml \cdot kg^{-1} \cdot hr^{-1}$) was begun. The left common carotid artery was exposed, and a stiff 8F (2.76 mm OD) polyethylene catheter was inserted and advanced to within 1 cm of the aortic valve for blood sampling and measurement of systemic arterial blood pressure with a Druck (Druck Ltd., Groby, Leicester, U.K.) pressure transducer.

A left thoracotomy was performed, and the fifth and sixth ribs were excised. The heart was then exposed and suspended in a pericardial cradle. The aortic root was dissected free of its fat pad, and an appropriately sized electromagnetic flow probe (Transflow 601, Skalar Medical, Delft, Holland) was placed around the aorta. A stiff 8F (2.76 mm OD) cannula was placed in the left ventricle via a stab wound into the apical dimple and attached to a Druck pressure transducer for left ventricular pressure measurement. A cannula was inserted into the pulmonary artery via the right ventricular outflow tract for determining cardiac output by dye dilution.

The left anterior descending coronary artery (LAD) was dissected free, and a 3.0 woven Dacron suture was placed proximal to the second major diagonal branch. The Dacron suture was then connected to a micrometer-controlled spring-suspended snare. A 2-mm electromagnetic flow transducer (Transflow 601, Skalar Medical, Delft, Holland) was placed around the artery proximal to the snare, and an occluder was placed distal to the flow transducer and used for periodic total coronary occlusion to obtain occluded zero flow readings. Two pairs of 5-MHz ultrasonic piezoelectric crystals were inserted into the left ventricular subendocardium by a previously described technique (2). One pair was implanted into an area near the apex supplied by the LAD distal to the dissected segment, and the other pair was placed into a basal area supplied by the left circumflex coronary artery (LC). Both pairs of crystals were placed parallel to the LV short axis (i.e., perpendicular to the line from the apical dimple to the aortic valve). Confirmation of correct placement of the LAD crystals within the area of ischemia, as well as placement of the LC crystals outside the ischemic territory, was obtained by observing regional function during a brief LAD occlusion. Dysfunctional contractile patterns present in the LAD but not the LC region confirmed not only proper crystal placement but also the absence of significant collateralization of the LAD region. The orientation and subendocardial position of the crystals were confirmed at necropsy.

Regional myocardial function was assessed by obtaining continuous measurement of segment length between each pair of crystals based on the measurement of ultrasonic transit times (7–9). Briefly, the instantaneous distance between a pair of 5-MHz crystals is proportional to the transit time of ultrasound because ultrasound at 5 MHz has a constant velocity of 1.56 mm/μs in the myocardium (8).

Aortic and left ventricular pressures were recorded, as well as aortic blood flow, stroke volume (obtained by integration of aortic flow), and LV dP/dt (the first derivative of left ventricular pressure). The signals were recorded on a Mingograf 81 eight-channel recorder (Elema Schonander, Stockholm, Solna, Sweden). Length measurement involved calculations of end-diastolic lengths (EDL) and end-systolic lengths (ESL). For determination of these lengths, the timing of end-diastole was taken as the first positive deflection of LV dP/dt. End-systole was defined as the point aortic valve closure occurred, that is, the point when aortic blood flow first returned to zero. All length recordings were taken at a paper speed of 250 mm/sec for precise determinations of the end of diastole and systole. Stroke volume was calibrated in vivo by simultaneous determinations of cardiac output by indocyanine green.

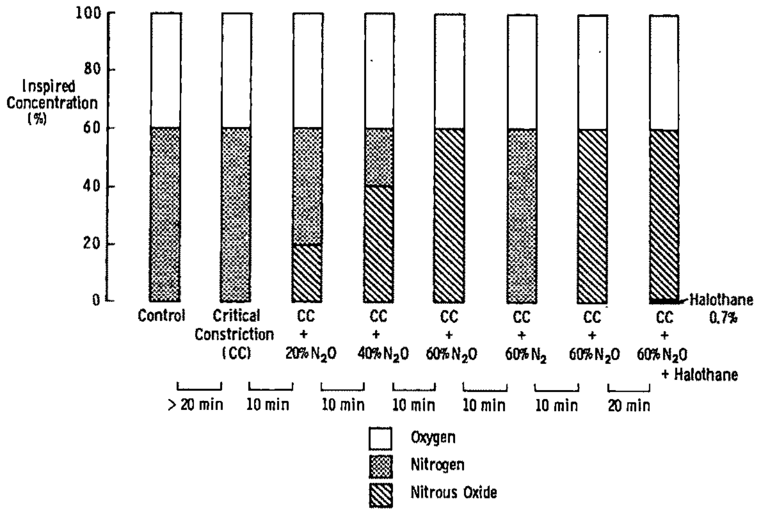

Figure 1. Graphic representation of the experimental protocol. Bars show the time interval between measurements.

Protocol

After completion of the surgical preparation, a 1-hour period of stabilization ensued. The halothane was discontinued immediately after the preparation was completed, and a bolus of 100 μg/kg IV fentanyl was given over 15 minutes. Intramuscular atropine 400 μg preceded the fentanyl injection by 15 minutes and was given to avoid profound bradycardia resulting from the large fentanyl bolus. After the loading dose of fentanyl, a constant infusion of 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was begun. The inspired oxygen concentration was maintained at 40% throughout the experimental protocol and was continuously measured with a paramagnetic oxygen analyzer (Taylor Servomex OA 272, Sybron Corp., U.K.). During this 1-hour period, instruments were calibrated, arterial blood gases analyzed, ventilation adjusted, and bicarbonate given as appropriate. Left ventricular end-diastolic pressure (LVEDP) was measured, and dextran (avg. mol. wt. 70,000) was given to maintain LVEDP above 5 mm Hg.

Following a series of control measurements, critical constriction of the LAD was imposed by tightening the micrometer-controlled snare until the postocclusive reactive hyperemia to a 10-second total occlusion of the LAD was abolished and there was no evidence of dysfunction in the LAD-supplied territory (2). After establishment of a stable critical constriction of the LAD, a 20-minute period without interventions or measurements was allowed to elapse, after which measurements were obtained. Nitrous oxide was then substituted for nitrogen in steps of 20% (inspired), the inspired oxygen concentration being held constant at 40% and continuously measured via the paramagnetic oxygen analyzer. Nitrous oxide concentrations were achieved by replacement of nitrogen with an appropriate amount of nitrous oxide by adjusting the fresh gas flow through the rotameters while maintaining a constant total fresh gas flow. Arterial blood gas tensions were measured 2 and 4 minutes after each increase in nitrous oxide concentration in seven dogs. Recordings were made 10 minutes after the nitrous oxide was increased, the end-tidal/inspired concentration ratio being 0.85–0.90 (10). After obtaining recordings at 20, 40, and 60%, the nitrous oxide was abruptly discontinued and replaced by nitrogen. Arterial blood samples were taken as above, and at 10 minutes another set of recordings were performed to quantify any residual effects of nitrous oxide and blood gas samples to reveal any diffusion hypoxia. Nitrous oxide was then administered directly at 60%, abruptly replacing all of the nitrogen, and blood gas samples were obtained. After 10 minutes, recordings were made. Halothane, 0.7% inspired, was then introduced. A period of 20 minutes was allowed to elapse before recording; this has been previously shown to result in a steady-state end-tidal concentration of 0.54 ± 0.05% (11). This concentration of halothane was employed because it would reduce the mean arterial blood pressures of the dogs to about 75 mm Hg. Figure 1 illustrates the experimental protocol.

Computation

At the conclusion of the experimental protocol, the LAD was cannulated and calibration of the LAD flow probe performed by injecting 5-ml aliquots of blood through the LAD cannula. After calibration, 5 ml of Evans blue was injected through the LAD cannula. The resulting area of stained myocardium, representing the territory supplied by the LAD, was separated from nonstained myocardium. The atria were removed and the stained ventricular myocardial fragments weighed, thus enabling LAD flow measurements to be normalized as milliliters per minute per 100 g of myocardium.

Mean arterial pressure (MAP) was calculated from the systolic and diastolic systemic arterial pressures (SAP, DAP). Coronary perfusion pressure (CPP) was calculated as the difference between DAP and left ventricular end-diastolic pressure (LVEDP). Cardiac output (CO) was calculated by multiplying stroke volume and heart rate.

Regional function was examined by calculating systolic shortening and postsystolic shortening. Systolic shortening (SS) was defined as the end-diastolic length (EDL) minus the end-systolic length (ESL) and expressed as a percentage of end-diastolic length to compensate for preload-induced changes of performance. Postsystolic shortening (PSS) was defined as the difference between ESL and the resultant minimum segment length attained during diastole. This is expressed as a percentage of the total segmental shortening to compensate for changes in inotropy. To compensate for small differences in the distance between the sonomicrometry crystals owing to placement, the initial (control) values of EDL in both the LAD and LC territories were given a value of 10 mm, and all other lengths were normalized accordingly (9).

Results were analyzed for statistical significance using two-way analysis of variance and Duncan's test or a paired *t*-test when appropriate. For analysis of controls, to determine any time-related differences or residual nitrous oxide effects, a one-way analysis of variance was used. Some parameters exhibited skewed distributions and thus were analyzed by the nonparametric Friedman two-way analysis of variance, Wilcoxon matched-pairs test, or Kruskal–Wallis one-way analysis of variance as appropriate. In all cases, $P < 0.05$ was considered significant.

Results

Comparison of Control with Critical Constriction

Table 1 illustrates the comparison between control values, obtained before critical constriction, and the two stages in which no nitrous oxide was present in the anesthetic. These two stages, noted as time 1 and time 2 in Table 1, differ with respect to time (40 minutes) and in the fact that at time 2 all of the dogs had received nitrous oxide administered in steps of 20% to a peak concentration of 60% over the preceding 40 minutes.

Table 1. Global Hemodynamic and Regional Myocardial Function Data with 40% O_2/60% N_2 and Fentanyl Anesthesia. Values are Mean ± SEM*

		Critical Constriction	
	Baseline	Time 1	Time 2
HR (beats/min)	128 ± 10	124 ± 9	106 ± 7
MAP (mm Hg)	129 ± 5	123 ± 4	117 ± 5
LVEDP (mm Hg)	9 ± 1	9 ± 1	10 ± 2
CPP (mm Hg)	107 ± 4	100 ± 4	92 ± 5
LV dP/dt_{max} (mm Hg/sec)	2250 ± 150	2100 ± 100	2050 ± 200
CO (L/min)	2.73 ± 0.35	2.43 ± 0.32	2.29 ± 0.26
CBF [$ml \cdot min^{-1} \cdot (100\ g)^{-1}$]	88 ± 16	76 ± 16	74 ± 16
LAD			
EDL (normalized) (mm)	10.0 ± 0.0	9.9 ± 0.1	10.0 ± 0.2
SS (%)	20.5 ± 2.9	17.0 ± 3.3	17.7 ± 2.4
PSS (%)	1.3 ± 0.9	4.2 ± 2.3	6.4 ± 2.6
LC			
EDL (normalized) (mm)	10.0 ± 0.0	10.0 ± 0.0	10.1 ± 0.2
SS (%)	13.5 ± 1.0	13.4 ± 1.0	13.5 ± 1.0
PSS (%)	1.9 ± 1.9	4.0 ± 2.8	6.8 ± 3.4

* No significant differences between any values by one-way analysis of variance (parametric or nonparametric, as appropriate).

Baseline: stage before establishment of LAD critical constriction. Time 1: after LAD critical constriction but before N_2O administration. Time 2: after critical constriction and gradual N_2O administration to 60% and before abrupt N_2O administration. Abbreviations: HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; CPP, coronary perfusion pressure; LV dP/dt_{max}, maximum positive value of the first derivative of left ventricular pressure; CO, cardiac output; CBF, left anterior descending coronary artery flow; EDL, end-diastolic length, normalized to a value at baseline of 10.0; SS, systolic shortening; PSS, postsystolic shortening.

The results show no significant differences between any of the values measured. Although dysfunction, observed as PSS, increased slightly with the application of critical constriction to the LAD, this difference was not significant. Critical constriction caused a small decrease in coronary blood flow (CBF), but this difference also was not statistically significant. No systolic bulge was seen in either segment.

Stepwise and Abrupt Administration of Nitrous Oxide

Data in Table 2 show values for global hemodynamics and regional function during both stepwise and abrupt addition of nitrous oxide. Heart rate (HR) decreased with gradual nitrous oxide administration, becoming significant at 60%. Significant decreases also occurred in MAP and LV dP/dt_{max}. The decrease in CBF was not significant. While EDL significantly increased in both the LAD (compromised) and LC (normal) segments, no significant changes in regional SS occurred with gradual nitrous oxide administration. No systolic bulge was seen in either segment.

Table 2. Global Hemodynamic and Regional Myocardial Function Data for Gradual Abrupt N_2O and Subsequent Halothane Administration to Narcotic-Based Anesthesia with LAD Critical Constriction. Values are Mean ± SEM

	Gradual				Abrupt		
N_2O concentration:	0%	20%	40%	60%	0%	60%	60% + HAL
HR (beats/min)	128 ± 10	124 ± 8	111 ± 7	104 ± 6*	106 ± 7	98 ± 5	107 ± 7
MAP (mm Hg)	123 ± 4	121 ± 5	118 ± 5	113 ± 4*	117 ± 5	106 ± 4‡	76 ± 6‖
LVEDP (mm Hg)	9 ± 1	9 ± 2	9 ± 1	10 ± 1	10 ± 2	10 ± 2	8 ± 1‖
CPP (mm Hg)	100 ± 4	100 ± 5	94 ± 5	89 ± 4	92 ± 5	83 ± 4	58 ± 6‖
LV dP/dt_{max} (mm Hg/sec)	2100 ± 100	1900 ± 150*	1750 ± 100*	1800 ± 150*	2050 ± 200	1700 ± 150‡	1000 ± 100‖
CO(L/min)	2.43 ± 0.32	2.49 ± 0.43	2.19 ± 0.24	2.06 ± 0.23	2.29 ± 0.26	1.86 ± 0.22‡	1.42 ± 0.20‖
CBF [$ml \cdot min^{-1} \cdot (100\ g)^{-1}$]	76 ± 16	69 ± 14	66 ± 16	63 ± 16	74 ± 16	57 ± 15§	42 ± 8
LAD							
EDL (normalized) (mm)	9.9 ± 0.1	10.2 ± 0.1*	10.3 ± 0.1*	10.4 ± 0.2*	10.0 ± 0.2	10.1 ± 0.2	10.1 ± 0.2
SS (%)	17.0 ± 3.3	16.6 ± 2.2	14.9 ± 2.2	15.0 ± 2.4	17.7 ± 2.4	15.8 ± 2.2	8.2 ± 2.5‖
PSS (%)	4.2 ± 2.3	10.3 ± 3.6	12.1 ± 3.9†	12.5 ± 3.6†	6.4 ± 2.6	9.9 ± 3.2§	30.8 ± 12.6#
LC							
EDL (normalized) (mm)	10.0 ± 0.1	10.2 ± 0.1*	10.3 ± 0.1*	10.4 ± 0.1*	10.1 ± 0.2	10.2 ± 0.2	10.1 ± 0.2
SS (%)	13.4 ± 1.0	13.2 ± 1.2	12.6 ± 0.8	13.4 ± 1.0	13.5 ± 1.0	13.5 ± 1.2	11.9 ± 1.5
PSS (%)	4.0 ± 2.8	5.2 ± 2.6	8.3 ± 3.2	4.8 ± 2.6	6.8 ± 3.4	6.2 ± 3.2	6.8 ± 4.8

*$P < 0.05$ vs 0% (gradual) N_2O by two-way analysis of variance and Duncan's multiple range test.
†$P < 0.05$ vs 0% (gradual) N_2O by Friedman two-way analysis of variance and Wilcoxon matched pairs test.
‡$P < 0.05$ vs 0% (abrupt) N_2O by paired *t*-test.
§$P < 0.05$ vs 0% (abrupt) N_2O by Wilcoxon matched pairs test.
‖$P < 0.05$ vs 60% (abrupt) N_2O by paired *t*-test.
#$P < 0.05$ vs 60% (abrupt) N_2O by Wilcoxon matched pairs test.
Abbreviations: 60% + HAL, 60% inspired nitrous oxide, and 0.7% inspired halothane added to narcotic anesthetic. Other abbreviations as in Table 1.

The abrupt administration of 60% nitrous oxide resulted in significant decreases in mean arterial pressure and LV dP/dt_{max}, similar to those seen with stepwise administration. Significant decreases in cardiac output (CO) and CBF also occurred, while HR remained unchanged. The decrease in coronary flow was of a similar magnitude to that observed with the gradual increase of nitrous oxide; comparison of the values for abrupt versus acute administration of 60% nitrous oxide showed no difference.

Regional SS was not significantly affected by abrupt nitrous oxide administration. The LC (normal) segment SS showed no differences after the abrupt addition of nitrous oxide, similar to the results seen with gradual nitrous oxide administration. No systolic bulge was observed in either segment.

Postsystolic shortening was observed in the compromised LAD region during 40 and 60% gradual nitrous oxide administration and during 60% abrupt nitrous oxide administration. There was no significant difference in the magnitude of dysfunction induced by 60% gradual nitrous oxide in comparison with 60% abrupt nitrous oxide (Fig. 2). The LC (normal) segment did not develop dysfunction with acute nitrous oxide administration, a result similar to that obtained with stepwise nitrous oxide.

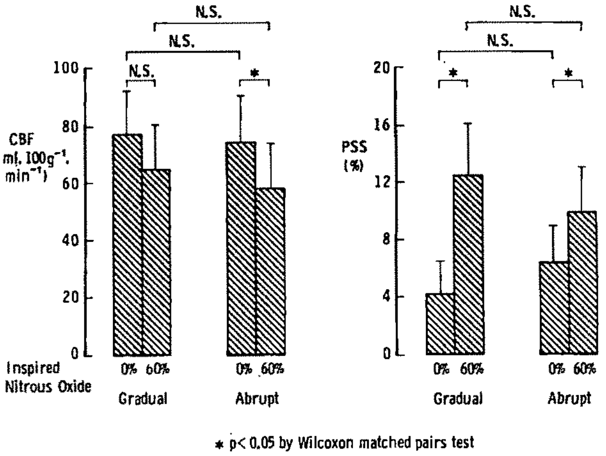

Figure 2. Coronary blood flow and PSS with gradual and abrupt 60% inspired nitrous oxide administration. Values are mean ± SEM.

Blood Gas Analysis

Seven dogs had arterial blood samples drawn for analysis during LAD critical constriction prior to nitrous oxide administration (time 1) and 2 and 4 minutes after each change in inspired nitrous oxide concentration. The PaO_2 values (mean ± SEM) during time 1 (baseline, 0% nitrous oxide) were 152.9 ± 9.1 torr (range 124–196) at 2 minutes, and 151.9 ± 9.6 torr (range 117–196) at 4 minutes. At 20% nitrous oxide, (172.1 ± 17.6 torr, range 130–263 at 2 minutes; 168.1 ± 17.5 torr, range 128–262 at 4 minutes), 40% nitrous oxide (172.7 ± 17.4 torr, range 130–261 at 2 minutes; 167.1 ± 16.9 torr, range 127–251 at 4 minutes), and 60% nitrous oxide (158.0 ± 15.1 torr, range 100–223, at 2 minutes; 156.4 ± 15.0 torr, range 100–

223 at 4 minutes), no significant changes in arterial oxygen tension occurred. Abrupt discontinuation of nitrous oxide caused a statistically significant but physiologically insignificant decrease in oxygen tension at 2 minutes but not at 4 minutes (140.1 ± 4.4 torr, range 118–157 at 2 minutes, $P < 0.05$, vs 20% and 40% nitrous oxide at 2 minutes; 141.8 ± 6.7 torr, range 127–172, at 4 minutes). The lowest individual value, 100 mm Hg, was seen in one dog at the 60% gradual nitrous oxide stage at 2 and 4 minutes.

Halothane

The addition of halothane (0.7% inspired) significantly decreased MAP, LVEDP, LV dP/dt_{max}, CPP, and CO. The significant fall in CPP was accompanied by a similar reduction in CBF that did not reach statistical significance.

Examination of regional function showed a significant decrease in SS, yet an unaffected EDL, in the LAD (compromised) territory. No significant decrease in LC function was seen. PSS in the LAD-supplied region was significantly increased with the addition of halothane (Fig. 3). LC (normal) segment dysfunction was minimal and did not change with halothane. No systolic bulge was seen in either segment.

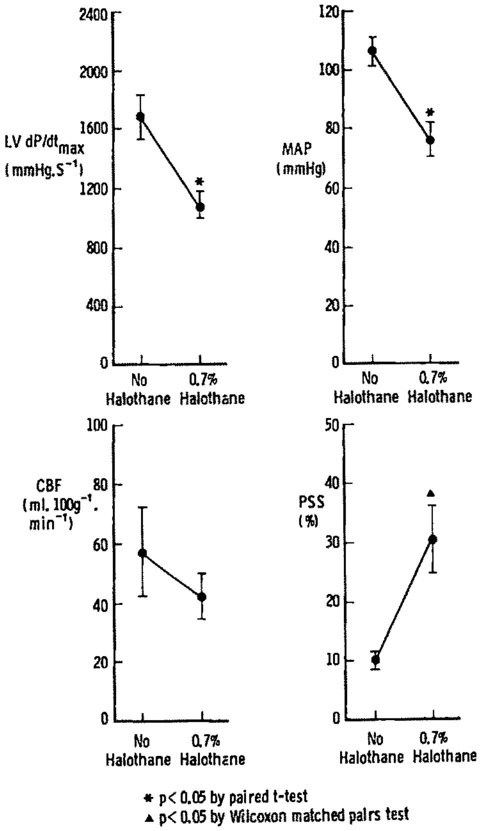

Figure 3. Changes in LV dP/dt_{max}, MAP, CBF, and PSS when halothane is added to 60% nitrous oxide/fentanyl anesthesia. Values are mean ± SEM. "No halothane" represents 60% nitrous oxide/40% O_2 with fentanyl 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ anesthesia. "0.7% halothane" represents anesthesia consisting of identical nitrous oxide and fentanyl dosages with 0.7% inspired halothane added.

Discussion

The common use of nitrous oxide to supplement narcotic anesthesia in patients at high risk of myocardial ischemia prompted us to examine the effect of nitrous oxide on regional function of myocardium with compromised blood flow. In a previous study we found that a significant amount of dysfunction (PSS) occurred when 66% nitrous oxide was added by acutely and completely replacing 66% nitrogen in the inspired gas mixture of dogs with compromised LAD blood flow. This dysfunction occurred irrespective of the synthetic narcotic used (fentanyl or sufentanil) (5). The present study was designed to duplicate the experimental conditions used in our previous study with a constant infusion of narcotic and a compromised myocardial segment obtained by critically constricting the LAD. However, we varied the protocol to determine whether a dose–response or threshold relation existed between nitrous oxide and regional dysfunction in the compromised myocardium.

PSS is a sensitive index and a consistent feature of ischemic regional dysfunction (2,3). However, PSS may occur with a normal coronary blood supply when calcium channel-blocking drugs are used with volatile anesthetics (6,12). PSS may be a mechanical manifestation of disruption of calcium ion fluxes, as ischemia (13) and calcium antagonists (14) both have effects on calcium fluxes. We chose not to use systolic thickening or SS as an indicator of ischemia because this can be affected by the inotropic state of the myocardium, which in turn is altered with anesthetic depth (15) and other negative inotropes, such as propranolol (9).

Our results show that PSS in compromised myocardium caused by nitrous oxide can occur with inspired concentrations as low as 40%. Furthermore, this dysfunction is apparently due to a threshold effect of nitrous oxide, rather than a dose response, and the dysfunction was unaffected by the rapidity with which the concentration was obtained. The mechanism of dysfunction induced by nitrous oxide remains obscure. We previously commented on the possibility that nitrous oxide had cellular or subcellular effects causing excitation–contraction uncoupling (5,16). This is further supported by the observation that intravenous calcium can reverse the hemodynamic effects of nitrous oxide (17), although the effect of calcium on nitrous oxide-induced regional dysfunction is not known. Alteration of subendocardial blood flow may also occur, as 60% nitrous oxide has been shown to constrict normal epicardial vessels (18). Although the effect of nitrous oxide on stenotic coronary vessels is not known, a further reduction in vessel diameter may exaggerate the reduction in distal coronary flow caused by critical LAD constriction and result in relative subendocardial underperfusion. Alterations in the transmural distribution of myocardial blood flow may occur, but because the blood flow distribution across the myocardium was not studied, no conclusion can be drawn with respect to this possible mechanism. Thus a local mechanism, possibly alterations in myocardial metabolism or local or transmural blood flow, is responsible for the appearance of regional dysfunction in compromised myocardium with nitrous oxide administration.

In comparing the two stages with 0% nitrous oxide and critical constriction, no differences were seen with regard to global or regional myocardial function (Table 1). Despite the performance of multiple coronary occlusions for calibration of the coronary flow probe, deterioration of LAD regional function and the appearance of regional dysfunction (PSS) did not occur. This suggests that neither time nor the number of acute coronary occlusions performed had an effect on the appearance of, or the increase in PSS. The lack of differences in global hemodynamics and regional function between time 1 and time 2 also suggests no lasting effect of nitrous oxide, unlike our previous findings (5). However, it may be that abrupt nitrous oxide administration has deleterious effects not apparent with stepwise or gradual administration.

The frequent sampling of arterial blood for oxygen tension was performed to exclude hypoxia as a mechanism for regional dysfunction. Diffusion hypoxia, associated with the abrupt discontinuation of a high concentration of nitrous oxide, has been reported (19,20). Our data agree with Rackow et al.'s calculations that an approximately 20% increase in Pa_{O_2} should occur as nitrous oxide diffuses into the blood, and their observation of a 20% decrease as nitrous oxide diffuses from the blood into alveoli (20). However, this decline did not achieve physiologic significance, because the oxygen tension never decreased below 100 mm Hg and thus a significant decrease in blood oxygen saturation or content presumably did not occur. Moreover, although gradual introduction of nitrous oxide resulted in a higher Pa_{O_2} than control at all concentrations administered, regional dysfunction increased in the LAD territory and decreased with the discontinuation of nitrous oxide. Thus hypoxia due to the abrupt discontinuation of nitrous oxide did not contribute to the dysfunction observed in the compromised myocardium.

Attempts have been made recently to examine the effect of nitrous oxide administration to patients with severe coronary artery disease by detecting wall motion abnormalities by echocardiography. Both studies concluded that nitrous oxide did not adversely affect regional myocardial function (21,22). However, in both of these studies, patients were undergoing coronary revascularization and thus may have been taking calcium channel-blocking drugs or β-adrenergic blocking drugs, both of which can cause alterations in regional myocardial function (6,23). Comparisons between two-dimensional echocardiography and endocardial sonomicrometry have been performed, and the limit of resolution of echocardiography was considered to be 1–2 mm in the axial view (24), whereas the resolution limit of sonomicrometry is 0.08 mm (9). The magnitude of PSS seen in the present study relative to total systolic shortening is small, significant changes occurring with an increase of 4–8%, which represents a change in length of 0.2–0.4 mm. Thus drug-induced alterations in regional wall motion and the small magnitude of change in PSS relative to the resolution capability of echocardiographic techniques may have obscured nitrous oxide's deleterious effects from detection by clinical echocardiography.

The third part of our protocol involved the addition of halothane, 0.7% inspired, to the anesthetic. This was done to simulate a situation frequently seen clinically: a hyperdynamic cardiovascular system despite high-dose narcotics and 60% nitrous oxide, which is treated with a volatile anesthetic. Roy et al. (25) suggested that an increase in the rate × pressure product associated, for example, with tracheal intubation, may cause myocardial ischemia. The concern that transient myocardial ischemic episodes are associated with perioperative infarction is supported by Slogoff and Keats (26). Merin (27) has commented that an important beneficial effect of volatile anesthetics in a situation of increased sympathetic outflow resulting from stress is that the myocardial oxygen supply/demand balance is restored by decreasing demand with the "depressant anesthetics," thus alleviating potentially deleterious transient myocardial ischemia. Indeed, Roizen and colleagues (28) found that the introduction of a volatile anesthetic decreased the hemodynamic indexes of myocardial ischemia during periods of surgical stress.

While adequate anesthesia was administered in all of our dogs (no movement despite the absence of muscle relaxants), MAP was still somewhat elevated.

Inspired halothane 0.7% was added to the anesthetic regimen to decrease the MAP to a level considered more acceptable in the clinical setting. Our intention was to decrease sympathetic activity and left ventricular wall tension, thus decreasing oxygen demand, while keeping coronary perfusion and global hemodynamics at an acceptable level. Halothane caused a reduction in CBF (−27%), but one in proportion to the decreases in hemodynamic determinants of myocardial oxygen demand (MAP = 28%; LV dP/dt_{max} −36%). A substantial increase in regional dysfunction of the compromised LAD segment occurred despite the apparent decrease in oxygen demand (Fig. 3). This agrees with our previous findings concerning the lack of preservation of myocardial oxygen supply/demand balance by halothane (2,3). Thus, in an animal preparation of critical coronary stenosis of the LAD, a low concentration of halothane added to fentanyl and nitrous oxide worsens dysfunction in the compromised myocardium.

These results suggest that halothane may not "normalize" the myocardial oxygen supply–demand relation in conditions of increased myocardial work. Buffington (4) has suggested that the MAP/HR ratio is an indicator of regional myocardial ischemia and that the adverse effects of halothane can be explained on the basis of halothane's actions on this ratio. Indeed this index was decreased by halothane in the present study (1.1 ± 0.1 to 0.7 ± 0.1, $P < 0.01$). However, there was no correlation between this index and PSS ($r = 0.34$, df = 14, $P > 0.1$). Roberts and coworkers (29) found that halothane, as compared to isoflurane, had a smaller toxic/therapeutic ratio with critical LAD constriction, and survival was not improved with mechanical increases in coronary perfusion pressure. These findings and the present study both suggest that halothane may have deleterious effects on the compromised myocardium by actions other than severe decreases in coronary blood flow. Transmural maldistribution, rather than a decrease in total myocardial blood flow, may explain the worsening of dysfunction in the compromised territory. Alternatively, halothane may alter excitation–contraction coupling by altering calcium ion fluxes, or halothane's effects may be due to an interaction with nitrous oxide, possibly altering local blood flow or calcium ion fluxes, which is deleterious to compromised myocardium.

In summary, 60% inspired nitrous oxide administration during narcotic-based anesthesia causes regional dysfunction whether administered gradually or abruptly. This dysfunction is small in magnitude and may not be detected by clinical echocardiography. Dysfunction is evident with 40% nitrous oxide and does not increase when nitrous oxide is increased to 60%, indicating that there is no dose–response relation between regional dysfunction and nitrous oxide at or above a 40% concentration. Administration of halothane to moderately depress global hemodynamics and myocardial oxygen demand in a hyperdynamic cardiovascular state did not protect but rather exacerbated the ischemic dysfunction seen with nitrous oxide.

We thank Mrs. A. L. Nunn for excellent assistance in the preparation of this manuscript.

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Sixty-Two Years Ago In

Anesthesia & Analgesia

J. G. Poe: The eye signs and their significance in general anesthesia. Current Researches in Anesthesia & Analgesia 1926;5:156–9.

In 1937 Arthur Guedel published a book entitled "Inhalation Anesthesia: A Fundamental Guide." A classic, it included popularization of the concept of stages or levels of general anesthesia, as well as the physical signs with which they are associated. Ten years before Guedel's book, however, this paper by Poe, an anesthetist at the Baylor Hospital in Dallas, described four stages of ether anesthesia: primary, intermediate, advanced, and progressively toxic. In greater detail than in Guedel's monograph, Poe goes on to describe six eye signs indicating the depth of general (ether) anesthesia: the conjunctivo-palpebral reflex, the lid muscular sign, the corneal reflex, the position of the eyes (recti muscular sign), pupillary reflex to light, and pupillary size. This article shows that recognition of the eye signs antedated Guedel's book, emphasizing yet again that rare indeed are the things that are totally new in science and medicine. This article also, however, reminds us how much systematic, direct, and conscientious observation of eye signs, even without ether, can tell us about a patient's condition. Mass spectrometers, oscilloscopes, ECGs, EEGs, and other monitoring devices are necessary and desirable. So, too, is patient contact with observation of physical signs, including eye signs.

Enhancement of Anesthetic Effect of Halothane by Spiradoline, A Selective κ-Agonist

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ALTHAUS JS, DIFAZIO CA, MOSCICKI JC, VONVOIGTLANDER PF. Enhancement of anesthetic effect of halothane by spiradoline, a selective κ-agonist. Anesth Analg 1988;67:823–7.

Reduction in the anesthetic requirement of halothane by narcotics has been studied extensively in humans and animals. Problems of respiratory depression, cardiovascular depression, muscle rigidity, and abuse potential make narcotics less than ideal as supplements to general anesthesia with inhalational agents. Spiradoline, a clinical candidate, is a highly potent and selective κ-agonist. As such it was considered important to study the effects of spiradoline on the minimum anesthetic concentration (MAC) of halothane required to block responses to noxious stimulation. The results of these experiments in rats showed a dose and plasma concentration-dependent reduction in halothane MAC over a wide range of subcutaneous doses of spiradoline (0.03 to 300 mg/kg). A maximum MAC reduction of 70% was obtained. Plasma levels of spiradoline (6 to 1800 ng/ml) were linearly related to dose. Measurement of blood pressure, heart rate, and P_{CO_2} determined over the course of each experiment showed minor variations which would be acceptable if observed in a clinical setting. It is concluded that spiradoline has promise as an anesthetic supplement.

Key Words: ANESTHETICS, VOLATILE—halothane. RECEPTORS, OPIOID—κ-. ANALGESICS—spiradoline.

Many drugs are used to supplement inhalational anesthetics. The purpose of such supplements is to increase the safety of anesthesia and to enhance control over cardiovascular responses to anesthesia and surgery, especially heart rate and blood pressure. Typically the newer synthetic narcotics are used for this purpose; however, side effects of respiratory depression and muscle rigidity make them less than ideal.

Spiradoline mesylate (U-62066E) (Fig. 1) is a potent, selective κ- (1) opioid agonist. Kappa-agonists are known to have analgesic properties but not to interact with μ-receptors (2). Thus, κ-agonists may be effective as supplements to anesthesia without addiction liability, respiratory depressant, or autonomic side effects of other available opioid analgesics. Use of κ-agonists also would identify the anesthetic contribution made by κ-receptors. The purpose of this study was to determine the potency of spiradoline as an anesthetic adjunct in rats by evaluating changes in the minimum anesthetic concentration (MAC) of an inhalational anesthetic (halothane) with increasing doses of spiradoline. In addition, the anesthetic interaction was further evaluated by monitoring respiratory depression and changes in cardiovascular function.

Methods

We evaluated the reduction of halothane MAC induced by spiradoline using the rat model described previously (3). Briefly, Sprague-Dawley rats (260–380 g) were each placed in a clear plastic cone and anesthetized with halothane (3.5% inspired) and oxygen for 3–5 minutes. Tracheal intubation was accomplished with a 16-gauge polyethylene catheter. Halothane was then decreased to 1.50% (inspired) and ventilation was controlled with a Harvard animal respirator, using measurement of arterial blood gases to assess and thus maintain normal P_{O_2}, P_{CO_2}, and pH. The femoral artery and vein were cannulated with PE50 tubing and the arterial catheter was connected to a Statham P23DB pressure transducer that

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Received from the University of Virginia Medical Center, Charlottesville, Virginia, and the Upjohn Company, Kalamazoo, Michigan. Accepted for publication April 12, 1988.

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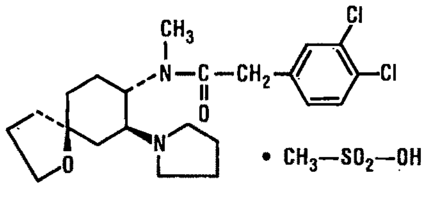

Figure 1. Structure of spiradoline mesylate, U-62066E, or (5α,7α,8β)-(±)-3,4-dichloro-N-methyl-N-(7-(1-pyrrolidinyl)-1-oxaspiro(4.5)dec-8-yl) benzeneacetamide methane sulfonate.

continuously recorded systolic and diastolic blood pressure and heart rate on a Grass Polygraph 7 recorder. Colonic temperature was monitored using a Yellow Springs thermistor, and normothermia was maintained with a heating blanket and lights.

For measuring alveolar anesthetic concentration, a fine polyethylene catheter (PE10) was introduced through and beyond the endotracheal tube until obstruction to passage was noted and then withdrawn 1–2 mm. Immediately before application of a noxious stimulus (see later), systolic and diastolic blood pressures and heart rates were noted for statistical analysis. Gas samples were obtained at this time by withdrawing 10 ml of gas through the catheter into a glass syringe over 3–5 minutes. The samples were then assayed by gas chromatography on a Varian model 3700 equipped with a flame ionization detector. A constant alveolar concentration of halothane was verified by analyzing triplicate samples.

Control MAC was established according to the method described by Eger et al. (4). A noxious stimulus was applied using a long hemostat clamped to full ratchet lock on the rat's tail for 1 minute. The tail was always stimulated proximal to a previous test site. Gross movement of the head, extremities, and/or body was taken as a positive response to stimuli; grimacing, swallowing, chewing, or tail flick were not. The halothane concentration (inspired) was decreased from 1.25% in increments of 0.2% to 0.25% until a positive response was elicited, allowing about a 12-minute equilibration after change in concentration. MAC was considered the concentration midway between the highest concentration (end-tidal) that allowed movement and the lowest concentration (end-tidal) associated with no movement. After each MAC determination, arterial blood gases were measured.

After a control MAC was established, the halothane concentration (inspired) was increased to 1.25%. Spiradoline was then administered subcutaneously in doses of either 0.03, 0.1, 0.3, 3, 10, 30, or 300 mg/kg. After drug administration, 30 minutes elapsed before the start of the MAC determination procedure. For each dose of spiradoline, the experiment continued an additional 50–70 minutes before MAC was established. Two doses of spiradoline were tested per rat beginning with the lower dose. At the completion of an experiment where 3 or 30 mg/kg was used as the test dose, animals were observed while spontaneously breathing 100% oxygen for 15 minutes. Blood gas tensions were then again measured.

Plasma obtained after each MAC determination was analyzed for spiradoline. Briefly, to 0.5 to 1.0 ml of plasma was added 1 μg U-69070E (benzeneacetamide, 3,4-dichloro-N-<4-(3-methoxypropyl)-2-(1-pyrrolidinyl)cyclohexyl>-N-methyl-,methanesulfonate, hemihydrate, (1.alpha.,2.beta.,4.beta.)-(.+−.)-), the internal standard. The pH of the plasma mixture was raised to about 8.5 with 100 μl of 0.1M sodium borate. The solution was loaded onto a Water's C18 cartridge and washed with distilled water. Spiradoline and the internal standard were eluted with 4 ml chloroform. A 100 μl volume of 0.1M sodium borate was added to the eluate, the mixture was shaken, and the organic layer was removed after the two phases formed. The organic layer was dried with heat and a stream of nitrogen gas. The residue was reconstituted in 125 μl of mobile phase and a 100 μl sample was analyzed by HPLC.

HPLC analysis of spiradoline and the internal standard was achieved with a Pecosphere 3X3 C-18 analytical column (Perkin-Elmer) coupled to an electrochemical detector. A glassy carbon working electrode set at 650 mV gave an optimal response. At a flow rate of 0.5 ml/min the retention times for spiradoline and the internal standard were about 7 and 9 minutes, respectively. The mobile phase consisted of acetonitrile (375 ml/L), tetrabutylammonium perchlorate (6 grams/L), disodium phosphate (3 grams/L), and the solvent was double distilled water. The pH of the solution was adjusted to 7.0 with phosphoric acid.

Linear regression was used to determine if plasma concentrations of spiradoline were linearly related to the subcutaneous doses given. Correlation (r) and probability were determined using standard techniques. Changes in blood pressures and heart rate between matched control and drug treatment groups were evaluated using paired *t*-testing. Differences were considered significant at $P < 0.05$.

Results

The halothane MAC for control rats in this study was 0.90 ± 0.01% (X ± SEM), which agrees with results

Table 1. Effect of Spiradoline Dose on Halothane MAC

Rat No.	MAC (% halothane)	Dose (mg/kg)	Decrease (%)	Group decrease (mean % + SEM)
1	0.79	0.03	1	0.16 ± 0.16
2	0.90	0.03	0	
4	0.89	0.03	0	
6	1.00	0.03	0	
7	0.88	0.03	0	
8	0.89	0.03	0	
5	1.03	0.10	12	8.80 ± 2.11
28	1.00	0.10	0	
29	1.00	0.10	13	
30	1.01	0.10	13	
31	0.96	0.10	5	
32	0.88	0.10	10	
2	0.90	0.30	15	16.83 ± 2.31
3	0.79	0.30	13	
6	1.00	0.30	23	
7	0.88	0.30	25	
9	0.88	0.30	13	
10	0.88	0.30	12	
3	0.79	3.00	30	25.50 ± 0.99
4	0.89	3.00	25	
8	0.89	3.00	25	
9	0.88	3.00	20	
10	0.88	3.00	23	
11	0.88	3.00	24	
5	1.03	10.00	35	37.00 ± 2.00
33	0.87	10.00	39	
24	0.78	30.00	32	45.16 ± 4.42
25	0.77	30.00	56	
26	0.90	30.00	36	
27	0.87	30.00	41	
28	1.00	30.00	59	
29	1.00	30.00	47	
30	1.01	300.00	71	70.50 ± 5.32
31	0.96	300.00	83	
32	0.88	300.00	54	
34	0.87	300.00	81	
35	0.77	300.00	79	
36	0.77	300.00	55	

previously reported for this model (3). MAC reduction was observed with the subcutaneous administration of spiradoline (Table 1). Between 0.03 and 300 mg/kg, the percent decrease in MAC was consistent within each group (N = 2 or 6). The group decreases in Table 1 appear in Figure 2 plotted as the log of spiradoline administered against percent reduction in halothane MAC. At high doses of spiradoline, the rate of change between percentage MAC reduction and dose was decreased between 30 and 300 mg/kg. In Figure 3, plasma concentrations of spiradoline measured by HPLC are plotted against dose. A straight line was fitted to the data by linear regression. A significant correlation coefficient of 0.9556 was determined.

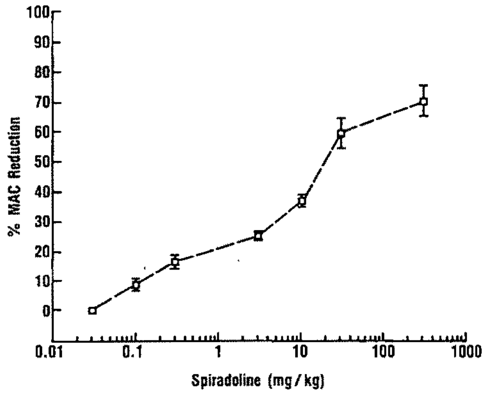

Figure 2. Dose-response curve relating percentage halothane MAC reduction and the dose of spiradoline at doses ranging between 0.03 and 300 mg/kg. Data plotted represents means ± SEM for two or six determinations. The corresponding control MAC values for each determination may be found in Table 1.

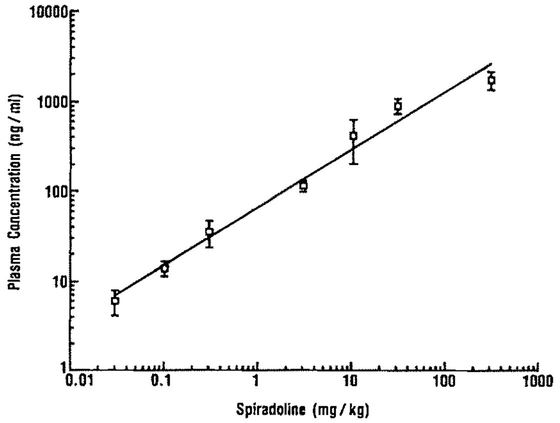

Figure 3. Linear regression analysis relating plasma concentrations of spiradoline to subcutaneous doses of spiradoline. Data plotted represents means ± SEM for two, six, or seven determinations. The straight line was fitted to the data using linear regression and the correlation coefficient was 0.9556 which is significant at $P < 0.0001$.

In Figures 4 and 5 the cardiovascular responses (observed immediately before tail clamp) to spiradoline are illustrated in terms of blood pressure and heart rate, respectively. At 0.03 mg/kg spiradoline, there was a small decrease in heart rate but there was no change in blood pressure. At 0.3 mg/kg, blood pressure began to decrease slightly, but at 3.0 mg/kg systolic blood pressure and heart rate were at control values. At 10, 30, and 300 mg/kg systolic blood pressure was not different from control; however, the diastolic blood pressure tended to be less than control. In terms of heart rate, only at 300 mg/kg was there greater than a 15% decrease compared to control.

Muscle rigidity with spiradoline was never observed and, consequently, mechanical ventilation adequately maintained carbon dioxide tension within a

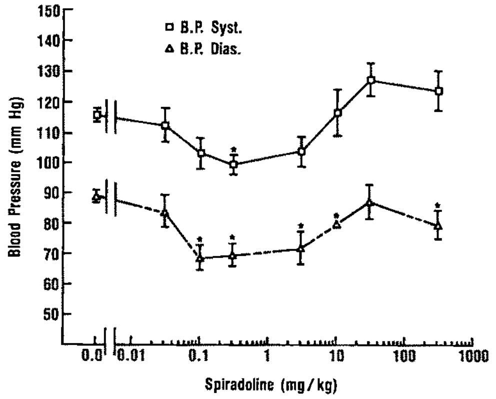

Figure 4. Systolic and diastolic blood pressure in rats related to spiradoline given a 0.03 to 300 mg/kg. The drug data plotted represents means ± SEM for two or six determinations. The mean ± SEM of the pooled controls is plotted at 0.00 mg/kg spiradoline for reference. Statistical differences (*) were based on comparisons between control values and test values found in the same rat. Differences were declared significant when $P < 0.05$ was found by paired *t*-testing.

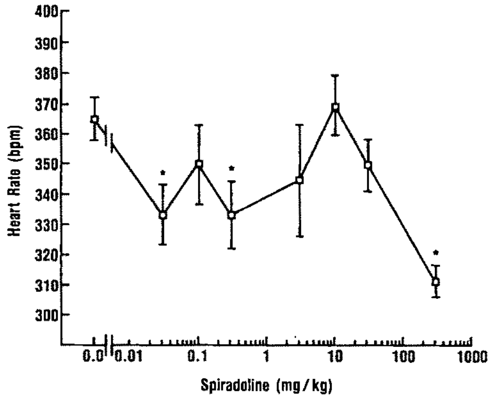

Figure 5. The rat heart rate in MAC determination experiments as related to spiradoline at 0.03 to 300 mg/kg. The drug data plotted represents means ± SEM for two or six determinations. The mean ± SEM of the pooled controls is plotted at 0.00 mg/kg spiradoline for reference. Statistical differences (*) were based on comparisons between control values and test values found in the same rat. Differences were declared significant when $P < 0.05$ was found by paired *t*-testing.

range of 42–47 torr. At the end of experiments in which doses of either 0.3 or 3 mg/kg were used, rats spontaneously breathed 100% oxygen for 15 minutes. Blood gas tensions were again measured and Pco_2 was found to have increased slightly. In 11 rats thus evaluated, the Pco_2 values increased as a group from 45.5 ± 1.7 to 48.7 ± 1.4 torr (X ± SEM).

Discussion

The pharmacology of opioids has been extensively reviewed by W. R. Martin (5). Both pharmacologic and binding studies have provided evidence of multiple opioid receptors. Opioid receptor nomenclature has become confusing although most researchers recognize the Greek letters delta, epsilon, kappa, mu, and sigma as designations of opioid receptor subtypes. Each receptor subtype can be differentiated pharmacologically and functionally. For example, selective agonists of delta, epsilon, kappa, mu, and sigma receptor subtypes are D-Ala2-D-Leu5-enkephalin, B-endorphin, U-50488H, morphiceptin, and SKF 10047, respectively. Kappa receptors are functionally unique because they do not increase neuromuscular activity, and they do not directly cause euphoria, cardiovascular depression and respiratory depression.

The search for a drug or combination of drugs that provide complete anesthesia while preserving hemodynamic stability has stimulated the development of synthetic narcotics. Morphine, fentanyl, and fentanyl derivatives all reduce the anesthetic requirement of inhalational anesthetics to various degrees (3,6–9). Unfortunately, each of these agents has side effects that result primarily from activation of μ-receptors. Morphine, in doses sufficient to supplement anesthesia with 60–67% nitrousoxide, is associated with hemodynamic instability and respiratory depression (10). Fentanyl and related compounds, although having less significant cardiovascular effects, nevertheless cause respiratory depression and muscle rigidity (9,10).

Another class of opioid drugs, the narcotic agonist–antagonists, have clinically useful analgesic properties because they act on both μ- and κ-receptors. One such drug, nalbuphine, does not have the severe cardiovascular and respiratory side effects typical of μ-agonists. Unfortunately, as an anesthetic adjunct, the effectiveness of nalbuphine is limited (9), reducing the MAC reduction of cyclopropane only 20% in rats (11). Spiradoline is one of the most potent and selective κ-agonists known (1). The affinity ratio for spiradoline comparing μ- and κ-binding was reported to be 1/84 (1). For this reason, it was viewed as a definitive test of the involvement of κ-receptors in the enhancement of anesthesia. Halothane was the anesthetic selected for study; however, caution must be taken when extrapolating our results to other inhalational agents. Spiradoline was effective at reducing halothane MAC over a wide range of doses (0.1 to 300 mg/kg). The greater potency of spiradoline as a supplemental agent to anesthesia as compared to other κ-acting agents such as nalbuphine (9) and U-50488H (12) can be demonstrated when considering threshold responses. A 10% reduction in cyclopropane MAC was achieved with nalbuphine at a plasma level of 110 ng/ml (9). An 8.8% reduction in halothane MAC was achieved with spiradoline at a plasma level of 14 ng/ml. As indicated above, however, caution must be taken when comparing the results of different inhalational agents. With U-50488H, no percent reduction in halothane MAC was observed at 3 mg/kg (13), whereas with spiradoline, a 25.5% reduction in halothane MAC was observed at this same dose. At higher doses (10 and 30 mg/kg), however, U-50488H and spiradoline gave nearly identical responses.

The results illustrated in Figure 3 indicated that at the doses tested, pharmacokinetically stable plasma levels of spiradoline were achieved at the point of MAC determination. Because the relation between dose and plasma levels was linear, it can be argued that the dose response curve in Figure 2 is also a reflection of the response to spiradoline in plasma.

Compounds such as spiradoline and U-50,488H lack μ side effects presumably because of κ-receptor selectivity. This selectivity is characterized by a lower sensitivity of κ-agonists than μ-agonists to antagonism by naloxone (2). The κ-agonist U-50488H exhibited this property when studied as an anesthetic adjunct (13). In like manner, only at high doses was naloxone found to completely reverse the anesthetic enhancing effects of spiradoline produced at 3 mg/kg (unpublished result).

One side effect, respiratory depression, thought to be related to activation of μ-receptors, would not be anticipated with κ-agonists. Lander et al. (14) showed that in sheep, epidural spiradoline resulted in significant analgesia with no respiratory depression with doses up to 120 μg/kg. In contrast, a double-blind study by Flacke et al. (9) comparing morphine, meperidine, and fentanyl, showed that as a group these compounds were associated with a 11-torr increase in P_{CO_2} over control values in humans. In our study, 3 and 30 mg/kg of spiradoline was associated with only a 3 torr increase in P_{CO_2} when animals were allowed to breathe spontaneously.

At 0.03 mg/kg spiradoline, there was a small but significant decrease in heart rate with no evidence of MAC reduction. This may have occurred because the cardiovascular response was more sensitive than the antinociceptive response to the effects of the analgesic. Alternatively this may reflect experimental variability; no significant decrease in heart rate was observed with 3 mg/kg spiradoline. The decreases in blood pressure at 0.3 mg/kg and 3 mg/kg, while statistically significant, would not be considered significant if encountered in a clinical setting.

In conclusion, our results show that spiradoline has promise as an anesthetic supplement and the role of κ-agonists for this purpose is further demonstrated.

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Tourniquet Pain During Spinal Anesthesia:

A Comparison of Plain Solutions of Tetracaine and Bupivacaine

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CONCEPCION MA, LAMBERT DH, WELCH KA, COVINO BG. Tourniquet pain during spinal anesthesia: a comparison of plain solutions of tetracaine and bupivacaine. Anesth Analg 1988;67:828–32.

The incidence of tourniquet pain was evaluated in 40 patients having orthopedic surgery of the lower extremities during spinal anesthesia using 15 mg of a plain solution of either 0.5% tetracaine or 0.5% bupivacaine. The drugs were administered in a randomized fashion, and measurement of the levels of sensory anesthesia to pinprick and motor blockade as well as the occurrence of tourniquet pain were made by an independent blinded observer. The onset and maximum cephalad spread of sensory anesthesia and the onset and degree of motor block were similar in both groups of patients. However, the duration of sensory anesthesia was significantly longer in patients in whom tetracaine was used. The incidence of tourniquet pain was significantly greater in patients given tetracaine (60%) than in patients given bupivacaine (25%). The occurrence of tourniquet pain was not related to the level of sensory anesthesia, because patients in the tetracaine group had a higher level of sensory anesthesia (mean T6) than did patients in the bupivacaine group (mean T10) at the onset of tourniquet pain. It is speculated that during spinal anesthesia both A and C fibers (mediating fast and slow pain, respectively) are initially equally inhibited. However, as the concentration of local anesthetic in the cerebrospinal fluid declines, C fibers may become unblocked earlier with tetracaine than A fibers, resulting in tourniquet pain in the presence of an otherwise satisfactory spinal anesthetic.

Key Words: ANESTHETICS, LOCAL—tetracaine, bupivacaine. PAIN—tourniquet. ANESTHETIC TECHNIQUES—spinal.

A pneumatic tourniquet is frequently employed in orthopedic surgery of the extremities to decrease bleeding and provide a clear surgical field. However, tourniquet-induced pain has been reported to occur in a significant number of patients during regional anesthesia despite the presence of otherwise adequate sensory anesthesia (1–5). The pain usually occurs between 45 and 60 minutes after inflation of the tourniquet (3). The pain is frequently described as a dull, ill-defined ache, the intensity of which increases until it becomes unbearable. Tourniquet pain during spinal anesthesia has been related to the dose of drug used (3), the level of sensory anesthesia (6), the local anesthetic employed (2–4), and the baricity of the spinal anesthetic solution (7).

It has been suggested that the incidence of tourniquet pain is less frequent in patients in whom bupivacaine has been employed for spinal anesthesia than in patients to whom tetracaine has been administered (2). However, these studies were not carried out with the specific intention of evaluating the incidence of tourniquet pain. In addition, isobaric solutions of bupivacaine were compared with hyperbaric solutions of tetracaine, and the dose of bupivacaine employed was greater than that of tetracaine (2). The current study was initiated to compare the incidence of tourniquet pain in patients in whom the same total dosages of plain solutions of 0.5% tetracaine and 0.5% bupivacaine were employed. Whereas in isolated nerve, Gissen et al. found tetracaine to be significantly more potent than bupivacaine (8), clinically these two drugs are frequently used in equal doses. This milligram-to-milligram comparison of the two agents is based on previous investigations that indicate that the potencies of the two drugs are similar (4,9,10).

Received from the Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication May 2, 1988.

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Table 1. Patient Characteristics

Agent	No.	Age (yr)	Sex	Height (cm)	Weight (kg)
Bupivacaine	20	62.2 ± 14.8	18F,2M	159.6 ± 10.6	71.0 ± 13.5
Tetracaine	20	64.4 ± 8.5	14F,6M	154.5 ± 9.2	71.0 ± 13.7

Values are mean ± SD.

Methods

The study was approved by the Human Research Committee of the Brigham and Women's Hospital, and informed written consent was obtained from all patients before their entry into the study. Forty patients who were scheduled for knee or ankle surgery requiring the use of a pneumatic tourniquet and for whom spinal anesthesia was planned were included in the study. All patients were classified as ASA status 1 or 2, and the age of the patients varied between 18 and 80 years (Table 1).

The patients were randomly assigned to receive either 15 mg plain 0.5% tetracaine solution or 15 mg plain 0.5% bupivacaine solution. All patients were premedicated with 5–10 mg diazepam orally approximately 1 hour preceding induction of anesthesia. Five hundred milliliters of lactated Ringer's solution was infused intravenously before the induction of spinal anesthesia. Blood pressure was recorded by means of an automated oscillometric device (Dinamap), and lead II of the ECG was continuously monitored. After baseline readings of blood pressure and pulse rate were obtained, the patients were placed in the lateral decubitus position with the operative side dependent. Under sterile conditions, lumbar puncture was performed at the L3–4 interspace with a 26-gauge needle. The appearance of clear cerebrospinal fluid in the hub of the needle indicated proper needle placement. Three milliliters (15 mg) of either 0.5% bupivacaine or 0.5% tetracaine solutions was injected over 30 seconds. All patients were kept in the lateral position for 2 minutes and then turned to the supine horizontal position. Sensory anesthesia to pinprick was evaluated at 2, 5, 10, 15, 20, and 30 minutes after the intrathecal injection of the anesthetic solution, and every 15 minutes thereafter, until all signs of sensory anesthesia had disappeared.

The degree of motor block was assessed on a 0 to 3+ basis as previously described (9). Motor block was evaluated at the same time intervals as the level of sensory anesthesia. However, motor block could not be assessed intraoperatively. Postoperatively, motor function was determined at 15-minute intervals until the return of full motor function. Blood pressure and pulse rate were measured 2 and 5 minutes after drug injection and then every 5 minutes intraoperatively and every 15 minutes postoperatively.

Evaluation of the extent of sensory anesthesia and the degree of motor blockade, as well as the presence of tourniquet pain, was performed by an investigator unaware of which spinal anesthetic agent had been administered. Intravenous diazepam in 1–2-mg increments was given for intraoperative sedation. Narcotics were not given intraoperatively unless the patient reported pain (see later).

The adequacy of anesthesia was determined on the basis of the patient's voluntary statement regarding the presence or absence of pain. Patients were also frequently questioned as to whether they were experiencing any discomfort. If the patient complained of pain, the patient was asked to describe the nature of the pain and to localize the pain. If the pain was described as a dull ache referable to the area of the tourniquet, it was recorded as tourniquet pain. The time of the onset of pain was recorded, as was the level of sensory anesthesia to pinprick at the time that pain occurred. Sensory anesthesia to pinprick in the S1 dermatomal level was assessed, when possible, in patients who developed tourniquet pain. Tourniquet pain was treated with IV fentanyl in 50–100-μg increments. If, in the opinion of the patient, the pain was unbearable despite the administration of fentanyl, general anesthesia was then induced.

The onset, spread, and duration of sensory anesthesia and the onset, depth, and duration of motor blockade in the two groups were analyzed for statistically significant differences by unpaired Student's *t*-tests. Differences in the frequency of tourniquet pain in the two groups were analyzed by means of χ^2 analysis or Fisher's exact probability test. $P < 0.05$ was considered statistically significant. Values are expressed as mean ± SD.

Results

No statistically significant difference existed between patients receiving intrathecal tetracaine or bupivacaine with regard to age, weight, or sex (Table 1). There was no difference in the time required for sensory anesthesia to reach the T12 dermatomal level in the two groups (Table 2). In addition, the maximum cephalad spread of sensory anesthesia and the time to achieve the maximum level were similar in the two groups (Fig. 1).

Duration of sensory anesthesia was significantly different in the two groups. The average time for regression of sensory anesthesia to the T12 dermatomal level was 232 ± 61 minutes in patients given

Table 2. Onset and Regression of Sensory Anesthesia

Agent	Time to onset of anesthesia to T12 (min)	Maximum cephalad level mean (range)	Time to maximum level (min)	Time to regression to T12 level (min)	Time to complete regression (min)
Bupivacaine	2.7 ± 3.9	T4 (T10–T1)	27 ± 14	198 ± 40	289 ± 54
Tetracaine	5.2 ± 4.8	T5 (T11–C7)	35 ± 20	232 ± 61	373 ± 104
Probability	NS	NS	NS	<0.05	<0.01

Values are mean ± S.D. NS, not significant.

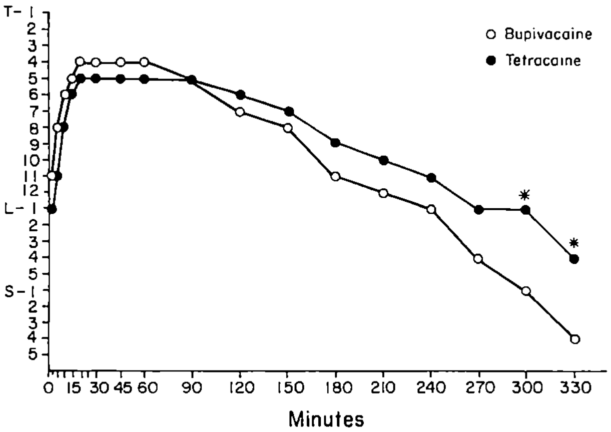

Figure 1. Cephalad spread and regression of sensory anesthesia. *$P < 0.05$, compared to bupivacaine.

tetracaine compared to 198 ± 40 minutes in patients given bupivacaine. The time to complete regression of sensory anesthesia was significantly longer in those patients receiving tetracaine (373 ± 104 minutes) than in patients who received bupivacaine (269 ± 54 minutes) (Table 2).

Thirteen of the 20 patients given tetracaine had inadequate anesthesia. One had inadequate anesthesia at the onset of surgery despite the fact that loss of sensation to pinprick was at the T6 dermatomal level at the time of incision. This patient was not included in the analysis of tourniquet pain. The other 12 patients with inadequate anesthesia developed tourniquet pain during surgery (incidence of 60%). In the bupivacaine group, 5 of the 20 patients developed tourniquet pain during surgery (25%) (Table 3). The difference in the frequency of tourniquet pain between the two groups was statistically significant (Table 3). The dermatomal level of sensory anesthesia at the time of tourniquet pain varied from T3 to L1 (mean T6) in the tetracaine group and from T6 to L1 (mean T10) in the bupivacaine group (Fig. 2). Although the incidence of tourniquet pain was significantly greater in patients given tetracaine, the sensory level of anesthesia at the time when tourniquet pain occurred was significantly higher in the tetracaine group than it was in patients having tourniquet pain in the bupivacaine group.

Sensory anesthesia at the S1 dermatomal level was assessed in 11 of the 17 patients who developed tourniquet pain. In all 11 patients, sensory anesthesia was present in the S1 dermatome and persisted well beyond the onset of tourniquet pain. Whether calculated from the time of intrathecal injection or from the time of tourniquet inflation, the onset of tourniquet pain occurred later in the bupivacaine group. The difference in tourniquet time at the onset of pain between the two groups was statistically significant. General anesthesia was required in four patients in the tetracaine group and in three patients in the bupivacaine group.

The onset and degree of motor blockade were similar in both groups. All but one patient in each group achieved complete motor blockade. Duration of motor blockade was significantly longer in the tetracaine group. Complete regression of motor blockade occurred in 314 ± 62.87 minutes with tetracaine compared to 263 ± 60.05 minutes with bupivacaine ($P < 0.05$). No difference in arterial pressure or pulse rate was observed between the two groups at any time during the surgical procedure.

Discussion

A pneumatic tourniquet is commonly used in orthopedic surgery of the extremities to decrease bleeding and facilitate surgery. Tourniquet-induced pain is frequently reported when surgery is performed during spinal or epidural anesthesia, usually during an otherwise adequate blockade (1–5,7).

Tourniquet pain has been related to dose of spinal anesthetic agent (3), baricity of spinal anesthetic solution (7), level of sensory anesthesia (6), and the spinal anesthetic agent itself (2,4). Several studies (2,4,9) have suggested that the incidence of inadequate anesthesia and/or tourniquet pain is greater with intrathecal tetracaine than with intrathecal bupivacaine. However, in these earlier studies, the solutions of bupivacaine and tetracaine employed differed in baricity and in dosage. In the current study, equal doses (15 mg) of plain solutions of tetracaine and bupivacaine were administered for

Table 3. Tourniquet (TQ) Pain

Agent	Frequency of TQ pain (%)	Time between injection and onset of pain (min)	Time between TQ inflation and onset of pain (min)	Sensory level at time of onset of pain mean (range)
Bupivacaine	25*	131 ± 25*	106 ± 26*	T10 (T6–L1)*
Tetracaine	60	119 ± 36	78 ± 37	T6 (T3–L1)

Values are mean ± SD.
*P <0.05.

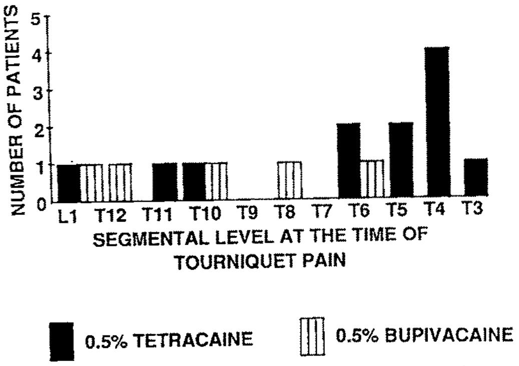

Figure 2. Segmental level at the time of onset of tourniquet pain. Twelve patients who received tetracaine (60%) and 5 patients who received bupivacaine (25%) developed tourniquet pain. At the onset of tourniquet pain, the mean sensory level of anesthesia in the tetracaine group was T6, and in the bupivacaine group it was T10.

spinal anesthesia. Our results confirm previous reports that the incidence of tourniquet pain is significantly greater in patients receiving intrathecal tetracaine than in those receiving intrathecal bupivacaine.

The etiology of tourniquet pain remains obscure. Several theories have been proposed to explain tourniquet pain. Cole (11) and Egbert and Deas (3) postulated that tourniquet pain involves activation of nociceptive fibers larger than those transmitting other types of pain. After induction of spinal anesthesia, the local anesthetic concentration in these larger fibers is believed to decrease more rapidly until the concentration is not sufficient to block the tourniquet-related stimulus. Egbert and Deas (3) were able to decrease the incidence of tourniquet pain by increasing the dose of tetracaine. On the other hand, De Jong and Cullen (6) proposed that tourniquet pain is transmitted by small nonmyelinated fibers traveling along the sympathetic trunks and entering the cord at a level cephalad to the sensory block. However, the level of sensory anesthesia does not appear to influence the incidence of tourniquet pain, because this phenomenon has been reported during both spinal and epidural anesthesia in patients with high thoracic and low cervical levels of sensory anesthesia (1,2,4). The results obtained in the current study also indicate that the frequency of tourniquet pain is not related to the level of sensory anesthesia to pinprick. The tetracaine group, which had a greater frequency of tourniquet pain than did the bupivacaine group, also had a significantly higher sensory anesthesia level at the time of onset of tourniquet pain. Moreover, the failure to observe a relation between the sensory level of anesthesia and the incidence of tourniquet pain in various other studies indicates that this explanation is not valid.

Tissue ischemia has also been invoked as the cause of tourniquet pain. However, Hageouw et al. (12) observed that tourniquet pain subsides almost immediately upon tourniquet deflation. They concluded that this does not support the contention that tourniquet pain results from tissue ischemia.

Other possibilities exist to explain the different effects of tetracaine and bupivacaine with regard to the incidence of tourniquet pain. There is general agreement that pain is transmitted by the smallest myelinated A fibers (A-delta) and by unmyelinated C fibers. A-delta fibers are responsible for the so-called "fast pricking" pain, whereas C fibers are responsible for "slow" persisting and poorly localized pain. Incisional pain is most consistent with the fast pain mediated by A-delta fibers, whereas tourniquet pain is more consistent with the pain sensation carried by the C fibers.

Gissen et al. (8) have shown that, in vitro, C fibers are more resistant to local anesthetic induced conduction blockade than are the larger A fibers. At high concentrations of tetracaine and bupivacaine, the action potential of both A and C fibers is completely suppressed. As the concentration of local anesthetic in the bath is decreased, C-fiber action potential amplitude returns to normal levels while the A-fiber action potential is still suppressed. However, the differential effect of tetracaine on A and C fibers was more marked than that of bupivacaine. These in vitro results may mimic the events following induction of spinal anesthesia. After administration of an adequate dose of local anesthetic intrathecally, both A and C fibers would be inhibited. As the concentration of local anesthetic in the CSF falls, C fibers may become unblocked before the A fibers, resulting in tourniquet pain in the presence of an otherwise satisfactory spinal anesthetic.

A final possibility involves the enhancement of local anesthetic activity in isolated nerves as the frequency of nerve stimulation increases (13). Differences apparently exist between the various local anesthetics with regard to the degree of frequency-dependent block (14). The potency of bupivacaine is markedly enhanced by an increase in the rate of nerve stimulation. Because the constant pressure of an occlusive tourniquet may result in an increased rate of firing of nociceptive fibers, the presence of even low concentrations of bupivacaine in these fibers may be sufficient for conduction blockade in most patients. On the other hand, if the anesthetic activity of tetracaine is less influenced by the rate of nerve stimulation, then low concentrations of this agent in the nerves would be insufficient to block these nociceptive fibers activated by a tourniquet. Studies of the frequency-dependent blocking characteristics of bupivacaine and tetracaine in isolated nerves support this hypothesis (see Stewart et al., this issue).

In summary, tourniquet pain is a frequent occurrence during an otherwise adequate spinal anesthetic. However, this phenomenon occurs less frequently when bupivacaine is employed for spinal anesthesia as compared to tetracaine. This difference in the incidence of tourniquet pain between the two drugs is unrelated to baricity, dosage, or level of sensory anesthesia.

The authors thank Ellen Murray, RN, and Usha Dhingra, MD, for assistance in the collection and analysis of the data.

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ANESTH ANALG 1988;67:833–7 833

Decreased Incidence of Tourniquet Pain during Spinal Anesthesia with Bupivacaine

A Possible Explanation

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STEWART A, LAMBERT DH, CONCEPCION MA, DATTA S, FLANAGAN H, MIGLIOZZI R, COVINO BG. Decreased incidence of tourniquet pain during spinal anesthesia with bupivacaine: a possible explanation. Anesth Analg 1988;67:833–7.

In a previous report, the incidence of tourniquet pain was found to be 25% with bupivacaine and 60% with tetracaine (P < 0.05) spinal anesthesia. On the other hand, tetracaine is more potent than bupivacaine in abolishing the single-compound action potential in vitro in isolated nerves. These conflicting observations may be reconciled if bupivacaine produced greater frequency-dependent conduction blockade of nerve action potentials. This hypothesis was tested in C fibers of isolated, desheathed rabbit vagus nerves. The nerves were supramaximally stimulated at frequencies of 9 or 15 Hz. After a control period, the nerves were exposed to bupivacaine (0.2 mM) or tetracaine (0.02 mM) for 30 minutes. The local anesthetics were then washed out by continuous constant-rate perfusion. The decline and recovery of the first and last action potential amplitudes of the train were measured. Bupivacaine and tetracaine produced similar depression of the first action potential of the 9-Hz and 15-Hz trains. However, bupivacaine caused a delayed recovery of the last action potential of the 15-Hz train but not of the 9-Hz train. These results show that bupivacaine produces greater frequency-dependent conduction blockade of C fibers than does tetracaine. These findings offer a possible explanation as to why spinal anesthesia with bupivacaine results in a lower incidence of tourniquet pain than tetracaine.

Key Words: ANESTHETICS, LOCAL: bupivacaine, tetracaine. PAIN—tourniquet. ANESTHETIC TECHNIQUES—spinal.

In a previous study, we found that glucose-free bupivacaine spinal anesthesia was more effective than was glucose-free tetracaine in preventing lower extremity tourniquet pain during orthopedic surgery (1; see also Concepcion et al., this issue, p. 828). Other investigators have made similar observations (2,3). The mechanism by which bupivacaine proves more effective than tetracaine in preventing tourniquet pain is unknown.

The degree of conduction blockade induced by local anesthetics is modified by the frequency of impulse traffic in the nerve (frequency-dependent conduction block) (4,5). Because pressure from a limb tourniquet during orthopedic surgery may cause increased nerve impulse traffic with time, and because tourniquet pain appears to occur about the time when the local anesthetic concentration would be declining in the nerve tissue, we investigated, in an isolated nerve preparation, the possibility that the superiority of bupivacaine over tetracaine may be the result of greater frequency-dependent conduction blockade.

Methods

The rabbits used in this study were housed in the Harvard Medical School, NIH approved, animal care facility in accordance with the "Guide for the care and use of laboratory animals" (DHHS publication no. (NIH) 78-23 revised 1978). Animals were also treated in accordance with the Harvard Medical Area

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Received from the Department of Anaesthesia, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts. Accepted for publication May 2, 1988.

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"Guidelines for animal care and use of laboratory animals." These experiments were conducted on the isolated, desheathed rabbit vagus nerve preparation. The method of dissection, the handling of the nerves, and the preparation of the HEPES-Liley solution and of the local anesthetic solutions used to bathe the nerves have been described in detail (6). All experiments were carried out at room temperature.

Once removed from the rabbit, the nerve was desheathed and mounted in a Plexiglass stimulation-recording chamber. This chamber consisted of two electrode compartments (each containing a pair of electrodes) at either end, separated by a perfusion well. The ends of the nerve were placed across the pairs of electrodes, and the center of the nerve traversed the perfusion well. Petroleum jelly dams isolated the perfusion well from the electrode chambers. The central portion of the nerve that crossed the perfusion well (10 mm in length) was continuously washed at a constant flow rate with HEPES-Liley solution. To keep the nerve from drying out during the study, the electrode chambers were filled with paraffin oil.

One pair of electrodes was used to electrically stimulate the nerve and the other pair of electrodes was used to record the resulting compound action potential. After being mounted in the chamber, the nerve was supramaximally stimulated with trains at 9 or 15 Hz for 1 second at intervals of 5 or 10 minutes. The stimulus duration was adjusted to 1 msec to elicit C-fiber action potentials (6). C fibers are believed to convey the electrical activity mediating tourniquet pain. The control amplitudes of the first and last compound action potentials of the train were determined, and the nerve was then allowed to equilibrate in the chamber for 30 minutes. After the equilibration period, the perfusate was switched to HEPES-Liley solution containing bupivacaine (0.2 mM) or tetracaine (0.02 or 0.2 mM) for 30 minutes (wash-in). After 30 minutes of perfusion with the local anesthetic, the nerve was perfused (washed out) with HEPES-Liley solution free of the local anesthetic until the first compound action potential amplitude of the train achieved at least 80% of the baseline value. In one nerve, the action potential amplitude did not recover to 80% of the control value, and this experiment was not included in the data analysis. The sequence of events during a typical experiment is shown in Figure 1.

Initially, experiments were conducted utilizing the 9-Hz stimulus frequency. This frequency was chosen as a first approximation of the amount of traffic that might occur during tourniquet pain (7). For this series of experiments, the concentrations of bupivacaine and tetracaine used to perfuse the nerves were 0.2 and 0.02 mM, respectively. These concentrations were chosen to depress equally (approximately 90% blockade) the first action potential amplitude of the train (6). Because the frequency of action potentials transmitted during tourniquet pain is not known, similar experiments were conducted utilizing a stimulus frequency of 15 Hz. The nerves were again perfused with 0.2 mM bupivacaine and 0.02 mM tetracaine. However, because bupivacaine and tetracaine are used at the same concentration during spinal anesthesia, additional experiments were conducted with 0.2 mM tetracaine. The experiments with 0.2 mM tetracaine were carried out using the 15-Hz stimulation because frequency conduction blockade was most apparent at this stimulation rate (see later).

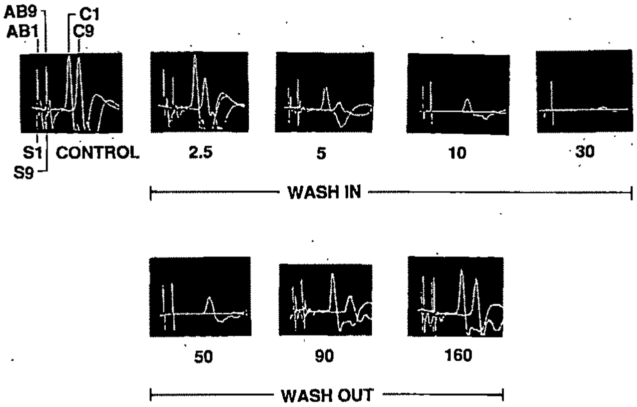

Figure 1. The sequence of events during a typical experiment. The panels show tonic and frequency-dependent conduction blockade of the C-fiber compound action potential from a rabbit vagus nerve exposed to 0.2 mM bupivacaine. Each panel is a photograph made from an oscilloscope recording, of superimposed traces of the first and ninth compound action potentials from a 9-Hz train. S1, AB1, and C1 are stimulus artifact, A- and B-fiber compound action potentials, and C-fiber compound action potentials, respectively, from the first stimulus of the train. S9, AB9, and C9 are stimulus artifact, A- and B-fiber compound action potentials, and C-fiber compound action potentials, respectively, from the ninth stimulus of the train. The number beneath each panel is time in minutes. After a 30-minute control period of perfusion with HEPES-Liley solution (not shown), a control photograph was obtained (0 time). The nerve was then perfused with HEPES-Liley solution containing 0.2 mM bupivacaine for 30 minutes. At 30 minutes, the bupivacaine perfusion was halted and the nerve was washed with bupivacaine-free HEPES-Liley solution. The washout continued until the first C-fiber compound action potential recovered to at least 80% of the control (100 minutes in this nerve). Note that frequency-dependent block persisted after 160 minutes of wash, indicated by C9/C1 < 1.0.

The changes in the compound action potential amplitude of the first and last action potentials, as a percentage of the baseline amplitude, were plotted against time. The difference in time required for 50% recovery between the last and the first action potential of the train was determined from the plots (see Fig. 2, lower plot). The choice of the time required for

50% recovery was made arbitrarily. These differences were averaged, and the mean values were assessed for significance utilizing Student's *t*-test. There were five nerves in each of the experimental groups. $P < 0.05$ was judged to be significant.

Results

The results of our initial experiments are shown in Figure 2 and Table 1. Figure 2 illustrates the wash-in and washout of 0.2 mM bupivacaine (upper plot) and 0.02 mM tetracaine (middle plot) on nerves stimulated at 9 Hz. The first action potential in bupivacaine-treated nerves recovered more rapidly than in those treated with tetracaine, despite the 10-fold higher concentration of bupivacaine. However, the times for the ninth action potential to achieve 50% recovery were the same (Table 1). Because of the disparate recovery times between the first and ninth action potentials, the difference in the time required for the first and ninth pulses to reach 50% recovery was greater in the nerves treated with bupivacaine (19 minutes for bupivacaine vs 9 minutes for tetracaine). This prolongation was, nevertheless, not statistically significant. The lack of significance is due to the large variance observed solely with the bupivacaine-treated nerves (see Table 1). We do not attribute the prolonged recovery to the higher concentration of bupivacaine, because similar rapid recovery occurred when the concentration of tetracaine was 0.2 mM and the nerves stimulated at a frequency of 15 Hz (18 minutes for tetracaine vs 71 minutes for bupivacaine—see later).

Similar experiments were performed at a stimulation frequency of 15 Hz. Figure 3 illustrates the results obtained with this frequency. The upper plot shows the response of nerves exposed to 0.2 mM bupivacaine, and the middle plot the response of nerves exposed to 0.02 mM tetracaine. At this stimulation frequency, the first action potential of the bupivacaine-treated nerves recovered more slowly than the tetracaine-treated nerves, but again this difference was not significant. However, the time required for the fifteenth action potential amplitude to reach 50% recovery and the difference in time for the fifteenth pulse and the first pulse to achieve 50% recovery was significantly different between the two groups (Table 1).

Because, in the clinical practice of spinal anesthesia, tetracaine and bupivacaine are routinely administered in equivalent doses, we also evaluated the effect of 0.2 mM tetracaine at the 15-Hz stimulation frequency. The effect of exposing nerves to this

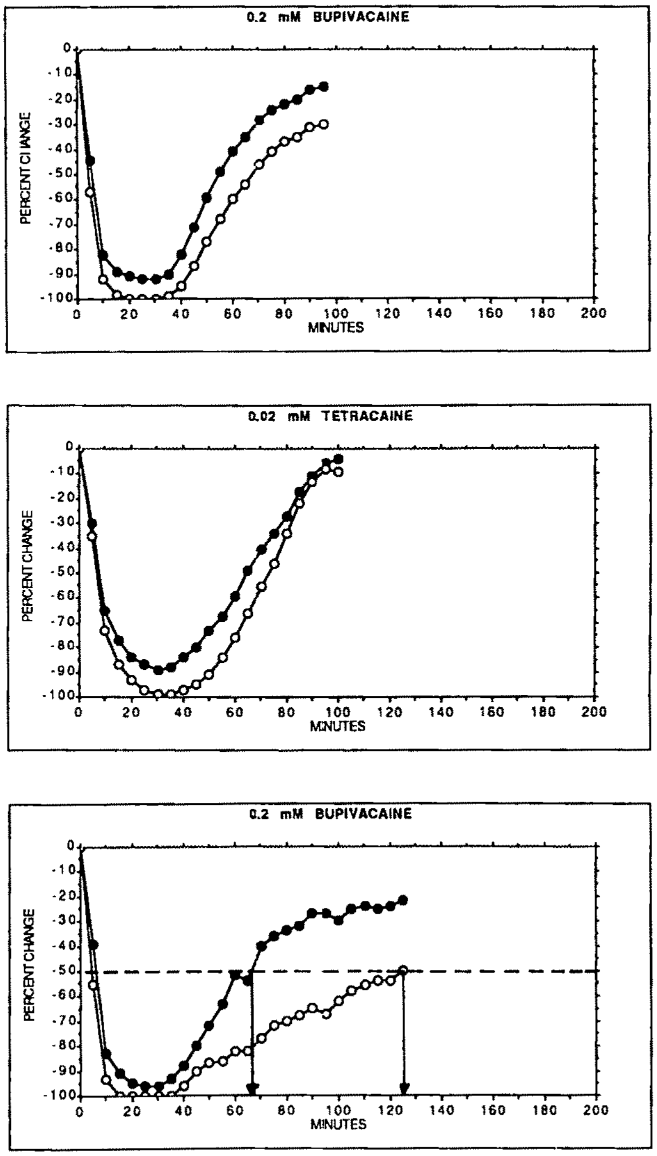

Figure 2. Onset and reversal of local anesthetic block of vagus nerves stimulated at a frequency of 9 Hz. The plots show the change in the C-fiber compound action potential amplitude (as a percentage of the control value) with time following perfusion with 0.2 mM bupivacaine or 0.02 mM tetracaine. The nerves were perfused with bupivacaine or tetracaine from 0 to 30 minutes. The washout with local anesthetic-free HEPES-Liley solution was started at 30 minutes and continued for the remainder of the study period. Upper plot, average of five nerves exposed to 0.2 mM bupivacaine; middle plot, average of five nerves exposed to 0.02 mM tetracaine; lower plot, single nerve exposed to 0.2 mM bupivacaine. This plot also illustrates the method used to calculate the difference in the time for the last and first pulse of the train to achieve 50% recovery. This value was calculated by locating the point on each curve during the washout that corresponds to 50% recovery. Perpendiculars were then dropped to the abscissa. The time corresponding to the earlier perpendicular was then subtracted from the time corresponding to the later perpendicular. The difference in this particular nerve was 125 − 68 = 57 minutes. (●) Percentage change of the first pulse of the 9-Hz train. (○) Percentage change of the ninth pulse of the 9-Hz train.

Table 1. Mean Time Required for the First and Last Pulse of the Train to Achieve 50% Recovery during Washout

Group	Drug	Conc. (mM)	Frequency (Hz)	Number of nerves	First pulse (min)*	Last pulse (min)*	Diff. (min)
A	Bupiv	0.20	9	5	28 ± 4†	47 ± 13†	19 ± 10†
B	Tetra	0.02	9	5	35 ± 2	44 ± 2	9 ± 1
C	Bupiv	0.20	15	5	58 ± 16	129 ± 28	71 ± 15
D	Tetra	0.02	15	5	36 ± 6	42 ± 5	6 ± 1
E	Tetra	0.20	15	5	88 ± 6	106 ± 7	18 ± 2

*Time is calculated from the time washout was begun (30 minutes).
†Values are means ± SEM.
Significant comparisons of differences: A v. C; $P < 0.05$; C v. D; $P < 0.01$; C v. E; $P < 0.01$; D v. E; $P < 0.01$.

concentration of tetracaine (0.2 mM) is shown in the lower plot of Figure 3. The effect of the higher tetracaine concentration was to cause greater conduction blockade and to delay the onset of the recovery of the compound action potential amplitude over that at 0.02 mM drug. Nevertheless, the difference in the time for the fifteenth pulse and the first pulse to achieve 50% recovery with 0.2 mM tetracaine (18 minutes) remained significantly less than that observed with 0.2 mM bupivacaine (71 minutes) (Table 1). Once recovery began, however, the return of the first and fifteenth action potential amplitudes toward control in the tetracaine-treated nerves were equally rapid, whereas this did not occur with bupivacaine (compare lower and upper plots of Figure 3). This phenomenon is even more dramatic if a comparison is made of the amount of recovery that occurred with 0.2 mM bupivacaine and 0.2 mM tetracaine late in the 15-Hz washout period. For example, at 180 minutes, the disparity in recovery between the first and fifteenth action potential amplitudes was 30% with bupivacaine (Fig. 3, upper plot) but essentially zero with tetracaine (Fig. 3, lower plot).

Discussion

Tourniquet pain during spinal anesthesia continues to be a problem for anesthesiologists and patients. The mechanism of tourniquet pain is uncertain. Some feel that tourniquet pain is mediated by sympathetic fibers that carry impulses paravertebrally around the spinal conduction blockade and enter the neuraxis above the level of spinal anesthesia (8). Another mechanism to explain tourniquet pain invokes the "gate" theory proposed by Melzack and Wall (9). In the latter theory, impulses in large afferent myelinated fibers inhibit the postsynaptic effect in the dorsal horn of impulses from smaller A-delta and C fibers, which are the fibers believed to mediate somatic pain. Strichartz and Zimmerman (10) have shown that in cat sural nerves exposed to lidocaine, the action potentials of large A-beta fibers are reduced at stimulation rates of 20–100 Hz, whereas the action potentials from the smaller A-delta and C fibers increase during repetitive stimulation at low frequencies (5–10 Hz). For C fibers, this effect was evident, even for trains of 40–50 pulses. Higher lidocaine concentration abolished this effect. These investigators postulated that tourniquet pain results from the combination of reduced A-beta fiber action potentials that thus block less effectively the postsynaptic effect of the impulses in smaller A-delta and C fibers, which are being relieved of block by chronic stimulation by the tourniquet.

At first glance, the results of this study appear to be contradictory to those of Strichartz and Zimmerman (10). In the continued presence of lidocaine, Strichartz and Zimmerman demonstrated relief of A-delta and C fiber conduction blockade with increasing stimulus frequency. The present study, on the other hand, was conducted during declining concentrations of bupivacaine and tetracaine and demonstrated greater frequency-dependent conduction blockade with bupivacaine but not with tetracaine as the stimulus frequency was increased from 9 Hz to 15 Hz. The use-dependent relief of C-fiber blockade demonstrated by Strichartz and Zimmerman (10) probably depends on the drug species and stimulus number as well as on frequency. Because of the differences in experimental design and local anesthetics employed in the two studies, we believe that the results are not necessarily in conflict. Additional studies are required to resolve this issue.

The purpose of this study was to determine whether or not the superiority of bupivacaine over tetracaine in reducing the incidence of tourniquet pain during spinal anesthesia may be the result of greater frequency-dependent conduction blockade with bupivacaine. The results indicate that frequency-dependent conduction blockade at 15 Hz but not 9 Hz is greater and more intense with bupivacaine than with tetracaine. Scurlock et al. (5) have also found

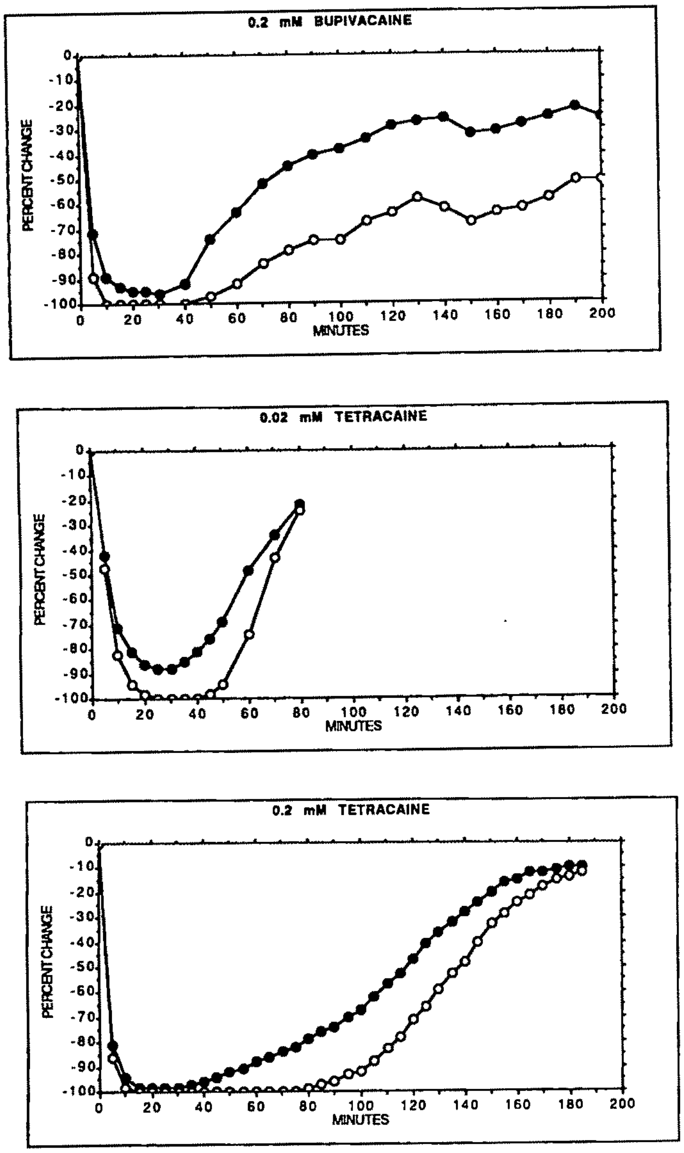

Figure 3. Wash-in and washout of vagus nerves stimulated at a frequency of 15 Hz. The plots show the change in the C-fiber compound action potential (as a percentage of the baseline value) with time following perfusion with (top to bottom) 0.2 mM bupivacaine, 0.02 mM tetracaine, and 0.2 mM tetracaine. The nerves were perfused with bupivacaine or tetracaine from 0 to 30 minutes. The washout with local anesthetic-free HEPES-Liley solution was started at 30 minutes and continued for the remainder of the study period. Upper plot, average of five nerves exposed to 0.2 mM bupivacaine. Middle plot, average of five nerves exposed to 0.02 mM tetracaine; all five nerves treated with tetracaine exhibited this rapid recovery of the first and fifteenth pulses. Lower plot, average of five nerves exposed to 0.2 mM tetracaine; the effect of increasing the concentration of tetracaine 10-fold was to cause greater conduction blockade and delay the onset and recovery of the compound action potential amplitude during the washout (compare to middle plot). Note that late in the washout period—for example, at 180 minutes—frequency-dependent conduction blockade persists with bupivacaine but is nearly absent with tetracaine. (●) Percent change of the first pulse of the 15-Hz train. (○) Percent change of the fifteenth pulse of the 15-Hz train.

that bupivacaine produces greater frequency-dependent conduction blockade than does tetracaine. Certainly, the perception of tourniquet pain when spinal anesthesia is wearing off is a more complex problem than the recovery of the action potential amplitude during the washout of local anesthetic from an isolated nerve. However, if the perception of pain is in part mediated by the frequency of action potentials conducted by peripheral nerves to the central nervous system, then the enhanced frequency-dependent conduction blockade seen with bupivacaine may contribute to the decreased incidence of tourniquet pain during spinal anesthesia with bupivacaine (see Concepcion et al., this issue) by limiting the number of action potentials entering the central nervous system.

We thank Dr. Gary Strichartz for suggesting this study and for much helpful criticism and advice during the preparation of the manuscript.

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1988;67:838–42

Pain Scores and Ventilatory and Circulatory Sequelae of Epidural Morphine in Cancer Patients with and without Prior Narcotic Therapy

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PFEIFER BL, SERNAKER HL, TER HORST UM. Pain scores and ventilatory and circulatory sequelae of epidural morphine in cancer patients with and without prior narcotic therapy. Anesth Analg 1988;67:838–42.

Pain scores and respiratory and circulatory sequelae of epidural morphine were studied in 25 patients with cancer, classified into two groups: 15 with and 10 without a history of previous narcotic analgesic therapy. Morphine, 2.5 mg initially and 5.0 mg 12 hours later, was given through an indwelling lumbar epidural catheter. Pain scores, heart rate, blood pressure, respiratory rate and minute volume, arterial P_{O_2} *and* P_{CO_2}*, and arterial pH were measured for 24 hours. Both groups had the same degree of analgesia after each epidural dose, suggesting that local morphine concentrations seen with epidural administration may be sufficient to overcome any degree of tolerance that may have developed at the spinal level during previous systemic narcotic administration. Statistically significant dose-dependent hypoventilation and concomitant respiratory acidosis were seen in both groups, the changes being significantly greater in opiate-naive patients. These results demonstrate that the ventilatory depressant actions of opioids are attenuated but not eliminated in narcotic-familiar cancer patients and that epidural narcotics are as effective in relieving pain in narcotic-naive patients as in patients previously exposed to narcotics for relief of cancer pain.*

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—morphine. ANALGESICS—morphine. PAIN, EPIDURAL—morphine.

Epidural morphine is an effective new approach to management of pain in patients with cancer. Occasional reports of late, life-threatening respiratory depression (1–4) and the demonstration of rostral spread of morphine in the cerebrospinal fluid (5,6) have, however, limited its use to patients who can receive careful monitoring of their ventilation. It has been our experience that clinically alarming respiratory depression is uncommon in patients previously given narcotic analgesics regularly for pain control (7–9).

A search of the medical literature failed to reveal any study that monitored respiratory and circulatory function of cancer patients over a 24-hour period after epidural morphine. Furthermore, no study has evaluated whether there is a difference in epidural narcotic management if a patient has already developed tolerance to opiates. The objective of this study, therefore, was to quantify and compare pain scores as well as respiratory and circulatory sequelae of epidural morphine in two groups of cancer patients: those already using narcotic analgesics and those who had been treated without them.

Methods

Twenty-five patients (17 male, 8 female) with chronic pain due to cancer gave informed consent for the study, which was carried out in accordance with the regulations of the Ethical Committee of the Philipps University of Marburg, West Germany, and the University of South Florida, Tampa. Carcinoma involved the rectum in eight patients, the colon in four, the prostata in seven, gynecologic sites in four, a hypernephroma in one, and a malignant melanoma in one. The mean age of the patients was 62.5 years (range 43–68); the average weight was 64.8 kg (range 52–74). The 25 patients were classified into two groups. Group A consisted of 15 patients treated with morphine hydrochloride IM or SC for an average period

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Received from the Department of Anesthesiology, University of South Florida, Tampa, Florida, and Philipps University, Marburg, West Germany. Accepted for publication April 26, 1988.

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of 8.6 weeks (range 2–16) before the study and an average daily dose between 40 and 120 mg. The last dose was administered on the evening before the study. Group B consisted of ten patients previously treated only with non-narcotic analgesics. Investigators were unaware of whether patients were in group A or B until analysis of the data was undertaken after clinical evaluations were completed.

The study was designed to accentuate the ventilatory and hemodynamic responses to epidural morphine. Therefore the two epidural morphine doses were timed so that the second injection would overlap and reinforce the depressant effects of the first.

An epidural catheter was placed in the usual manner at L3–4 in all 25 patients between 7 and 8 o'clock in the morning to minimize diurnal variations of the study variables. Correct placement was confirmed by injection of 4 ml bupivacaine 0.5% 2 hours before morphine injection. Two doses of morphine hydrochloride, initially 2.5 mg and 12 hours later 5.0 mg, were added to saline to a total volume of 10 ml and then injected into the epidural space via the indwelling epidural catheter. No other analgesics were administered during the study.

The variables studied included systolic and diastolic blood pressures (BP), heart rate (HR), respiratory rate (RR), ventilatory minute volume (VE), pain scores (PS) using a visual analog scale (0 = no pain, 10 = maximum pain), arterial blood gas tensions of oxygen (Po_2) and carbon dioxide (Pco_2), and arterial pH.

Measurements of these variables were made before placement of the epidural catheter; these served as the baseline values. Subsequent measurements of BP, HR, RR, and VE were made at 2, 4, 8, 12, 14, 16, 20, and 24 hours. The Po_2, Pco_2, pH, and PS were measured at 4, 12, 16, and 24 hours.

Blood pressure was measured by Korotkoff sounds using sphygmomanometry. Heart rates were taken from continuously recorded ECGs. Respiratory variables were measured using dry gas respirometry for 3 minutes. Arterial blood samples were taken from the radial artery and analyzed using an ABL II blood gas analyzer (Radiometer, Copenhagen).

Statistical Analysis

Repeated measures analyses of variance were calculated for all variables to evaluate the differences before and after drug administration. If this indicated a statistically significant change, multiple paired *t*-tests were used to identify the period when the corresponding variable had changed. Percentage changes relative to the baseline level were calculated for all variables. We used *t*-tests to compare the percentage changes between the two groups. $P <$ 0.01 were considered to indicate statistical significance.

Results

Group A: Previous Narcotic Use (Table 1)

None of the 15 patients in group A developed symptoms of narcotic withdrawal during the study. Pain scores decreased significantly, by about 60%, at 4 hours after the initial morphine dose and then further declined to 70% below baseline levels after the second dose. There were no significant changes in HR and BP during the 24-hour study. Respiratory rate decreased significantly, by about 15%, 8 hours after the second dose of morphine, and remained decreased through to the end of the study. Ventilatory minute volume declined statistically significantly, by about 8%, at 4 hours after the second morphine dose, and then returned to the baseline levels by the end of the study period. The Pco_2 increased significantly, by about 8%, at 4 hours after the second morphine dose and remained elevated throughout the rest of the study. The Po_2 showed no significant changes. Arterial pH was significantly below baseline levels only when measured 4 hours after the second dose, at which time the difference was 0.03 pH unit.

Group B: No Prior Narcotic Use (Table 2)

Pain scores in group B were significantly lower at all times after each epidural injection. The first morphine injection decreased the pain score by about 59% at the 4-hour measurement; 4 hours after the second dose, the pain score was further reduced to 72% below baseline levels. There were no significant changes in HR or BP throughout the 24-hour period. Respiratory rate decreased by about 8% at 4 hours after the first morphine dose and was further reduced to about 14% and 19% below baseline levels 2 hours and 4 hours, respectively, after the second morphine injection. This decrease in RR persisted throughout the remainder of the study. Ventilatory minute volume decreased significantly, by about 8%, 8 hours after the initial morphine dose. The second morphine dose decreased the VE further to 14% below baseline levels. Arterial Pco_2 increased by about 8% after the first morphine dose and by about 22% after the second injection. The Pco_2 remained elevated until the end of the study. Arterial Po_2 did not change

Table 1. Effect of Epidural Morphine (2.5 and 5.0 mg) in Cancer Patients Previously Receiving Opiates—Group A (Mean ± SD)

	Baseline	2 hr	4 hr	8 hr	12 hr	14 hr	16 hr	20 hr	24 hr
Pain score	5.9	—	2.4	—	3.5	—	1.7	—	3.2
	0.98	—	1.13	—	1.19	—	0.79	—	1.03
HR (beats/min)	78.1	77.1	76.5	77.7	79.3	76.3	76.5	79.3	80.7
	9.4	9.4	9.5	9.1	9.2	8.1	8.7	7.3	7.1
BP_{syst} (mm Hg)	134	131	129	134	136	129	128	135	137
	12.3	13.2	15.1	12.2	15.2	13.1	13.2	12.1	12.2
BP_{diast} (mm Hg)	79.6	82.8	81.1	82.7	83.9	80.7	83.9	84.0	84.0
	12.9	9.6	8.9	6.4	7.2	6.8	7.1	6.5	8.8
RR (counts/min)	15.6	14.6	14.7	15.4	14.9	15.9	14.5	13.2	13.7
	1.7	1.8	1.8	2.0	1.7	1.7	1.7	0.8	0.8
VE (L/min)	8.39	8.21	8.13	8.28	8.70	7.98	7.70	8.20	8.44
	0.63	0.50	0.49	0.51	0.57	0.46	0.49	0.57	0.65
Pco_2 (mm Hg)	43.9	—	45.3	—	45.3	—	47.4	—	46.5
	2.8	—	2.4	—	2.4	—	2.6	—	3.1
Po_2 (mm Hg)	84.9	—	82.1	—	83.0	—	79.3	—	80.6
	5.7	—	5.5	—	5.7	—	4.9	—	5.5
pH	7.41	—	7.39	—	7.39	—	7.38	—	7.39
	0.03	—	0.02	—	0.01	—	0.02	—	0.02

Abbreviations: HR, heart rate; BP_{syst}, systolic blood pressure; BP_{diast}, diastolic blood pressure; RR, respiration rate; VE, ventilatory minute volume.

Table 2. Effect of Epidural Morphine (2.5 and 5.0 mg) in Cancer Patients Not Receiving Opiates Previously—Group B (Mean ± SD)

	Baseline	2 hr	4 hr	8 hr	12 hr	14 hr	16 hr	20 hr	24 hr
Pain score	6.4	—	2.6	—	4.1	—	1.8	—	3.6
	1.36	—	1.62	—	1.92	—	0.65	—	1.42
HR (beats/min)	83.4	81.5	81.3	81.7	82.8	81.3	81.5	83.0	82.4
	10.5	10.2	9.9	10.3	8.9	10.8	8.1	10.6	10.1
BP_{syst} (mm Hg)	132	130	129	129	136	131	128	132	136
	18.2	14.1	13.6	15.2	13.2	13.4	14.2	17.0	12.2
BP_{diast} (mm Hg)	83	79	79	85	87	83	81	84	84
	13.2	9.8	7.9	6.2	6.1	6.1	6.3	9.1	8.2
RR (counts/min)	16.8	15.7	15.5	16.1	15.9	14.4	13.6	14.3	14.8
	1.6	1.7	1.9	1.4	2.2	1.3	1.9	1.7	1.2
VE (L/min)	9.27	8.96	8.80	8.56	8.98	8.43	7.95	8.24	8.49
	1.33	1.21	1.09	0.98	1.01	0.91	0.88	0.44	0.36
Pco_2 (mm Hg)	41.4	—	44.8	—	43.4	—	50.4	—	50.2
	2.7	—	3.2	—	2.3	—	2.9	—	1.5
Po_2 (mm Hg)	83.2	—	81.8	—	82.3	—	79.6	—	81.4
	4.2	—	3.9	—	4.3	—	3.2	—	3.7
pH	7.41	—	7.39	—	7.39	—	7.37	—	7.38
	0.02	—	0.02	—	0.02	—	0.01	—	0.01

Abbreviations as in Table 1.

significantly. Arterial pH significantly decreased by 0.04 pH unit at 4 hours after the second morphine dose and remained at this lower level for the remainder of the study.

One patient was excluded from the study because of marked respiratory depression requiring naloxone intervention. This happened in a 47-year-old group B patient with lung metastasis in whom the Pco_2 increased by about 30% while his VE and RR decreased by about 24 and 28%, respectively. The hypoventilation in this case was due to the slower respiratory rate, not changes in tidal volume. This patient had neither respiratory arrest nor loss of alertness. Predictably, naloxone increased his ventilation promptly; his Pco_2, Po_2, and pH returned gradually to normal levels by the end of the study.

Differences between Groups A and B

Changes in VE were significantly different in the two groups 8 hours after the first morphine dose and 4, 8, and 12 hours after the second dose. Patients in group A had significantly smaller decreases in VE than did patients in group B. There were significant intergroup differences in RR 4 hours after the second morphine dose, with significantly smaller decreases noted in group A patients. Changes in Pco$_2$ were significantly different in the two groups: Pco$_2$ increased significantly more in group B than in group A after the second morphine dose. Arterial pH was significantly different in the two groups only 4 hours after the second morphine dose. Group B had lower pH values than did group A at that time. There were no significant intergroup differences during the study in HR, BP, Po$_2$, or pain score.

Pruritus and nausea and vomiting occurred in four patients, one in group A and three in group B. Pruritus without nausea and vomiting occurred in one patient in group A and in two patients in group B. Nausea and vomiting without pruritus occurred in one patient in group B. Urinary retention was not observed.

Discussion

The development of tolerance to opioids limits their use in patients with chronic pain (8, 10–12). The opiate-familiar patients in this study did not show tolerance with respect to pain relief, which is in accordance with reports by Glynn and Mather (13) as well as Findler et al. (14) and Zens et al. (15), demonstrating that tolerance is not an inevitable consequence of prolonged treatment of chronic pain with systemic or epidural opioids. However, the opiate-familiar patients had significantly less respiratory depression and other side effects than opiate-naive patients. The epidural route delivers spinal concentrations of morphine that may be sufficient to overcome any subtle differences in receptor status, whereas the concentrations of morphine as it spreads rostrally to the respiratory centers in the brainstem are much lower and are closer to the concentrations produced by systemic administration. This would explain why tolerance was evident here for respiration and not for analgesia.

Respiratory depression after single epidural narcotic injection is described in the literature as bimodal, most pronounced at roughly 8 and 18 hours. The second dose in this study was timed so the bimodal peaks would overlap and reinforce the depressant effects of the first dose. It is not surprising, then, that the reaction to the second dose was greater hypoventilation and acidosis in both groups, although the response was attenuated in patients with tolerance due to previous opiate therapy. The significant respiratory depression among group A patients is in contradistinction to several reports (16–18) that describe no significant changes in respiratory function in narcotic-familiar cancer patients using doses very similar to the regimen in our study. Unfortunately there is little information in those studies as to how closely respiratory function was monitored. The more pronounced depression of VE and RR in group B indicates a higher sensitivity to morphine's respiratory depressant actions in opiate-naive patients.

The intergroup differences observed in Pco$_2$ demonstrate that respiratory function is depressed to a greater extent in opiate-naive than in opiate-tolerant patients, given the same dose of epidural morphine. The 22% increase in Pco$_2$ in opiate-naive patients after the second morphine dose is comparable with results obtained by Madsen et al. (19) and by Malins et al. (20) in surgical patients considered to be opiate-naive. Notably, Pco$_2$ increased in our study by about 9% in group A patients, who were assumed to have tolerance to narcotic analgesics.

Although the magnitude of changes found in the respiratory variables may be of borderline clinical importance, the concomitant changes in Pco$_2$ and pH indicate a clear impact on homeostatic regulations. Opiate-naive patients experienced a more pronounced challenge to their homeostasis after epidural morphine than did opiate-familiar patients. The group difference in arterial pH parallels the increases in Pco$_2$ for groups A and B and indicates less respiratory acidosis in opiate-tolerant patients. The undue sensitivity to epidural morphine shown by the one patient with pulmonary metastasis indicates that carefully reduced epidural narcotic dosage is necessary for the elderly and for those with pulmonary metastases. Opiate-familiar patients can be considered to be at lower risk for life-threatening hypoventilation than opiate-naive patients after epidural narcotics.

The stability of HR and BP in both groups A and B after epidural morphine is consistent with the findings of Yaksh and Noueihed (21) as well as those of Bromage et al. (22). As for other side effects, the incidence rates of pruritus (12%) and nausea and vomiting (4%) among our patients is comparable with findings reported by Zens et al. (7). The fact that three of the four patients exhibiting these side effects were in group B further points to the development of tolerance among group A to morphine's central effects.

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ANESTH ANALG
1988;67:843–8

Incidence and Etiology of Failed Spinal Anesthetics in a University Hospital:

A Prospective Study

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MUNHALL RJ, SUKHANI R, WINNIE AP. Incidence and etiology of failed spinal anesthetics in a university hospital: a prospective study. Anesth Analg 1988;67:843–8.

Two recent retrospective reports on the incidence of failed spinal anesthetics that indicated extremely variable results prompted the present prospective study of 200 consecutive spinal anesthetics to determine the incidence and causes of failed spinal anesthetics.

Tetracaine was the spinal anesthetic agent utilized in all cases—crystalline tetracaine (Niphanoid) in 71% and a 1% solution in 19% of the cases. The failure rate overall was 4%, with all failures being due to anesthetic factors, both technical and pharmacologic. However, only 25% of the failures were due to errors in technique, and 75% were due to errors in judgment with respect to pharmacologic factors (dosage, use of epinephrine, and/or positioning of the patient). Our data, therefore, differ from those of Levy et al. (Anesth Analg 1985;64:705–10), both in terms of failure rate, which is 25% of theirs, and in terms of causation, with our data indicating errors in judgment to be the causative factor three times as often as errors in technique. Presumably, this difference is due to the greater experience in spinal anesthesia that a resident receives at our institution.

Key Words: ANESTHETIC TECHNIQUES—spinal.

The issue of failed spinal anesthetics was recently rekindled by two retrospective studies of spinal anesthesia, one in a large university teaching hospital (1) and the other in a smaller community hospital (2). We believed that the 17% failure rate reported in the former study was unacceptable regardless of the size or type of hospital. Because retrospective studies are frequently based on incomplete and/or less detailed information, they might provide misleading information. Therefore we undertook the present study in an attempt to provide more accurate (and realistic) data concerning spinal anesthesia failures and the factors that contribute to them.

Methods

Two hundred healthy consenting adult patients scheduled to undergo surgery under spinal anesthesia were included in this study, which extended over the 6-month period from September 1985 through February 1986. Preanesthetic medication was left to the discretion of the patient's anesthesiologist and was individualized for each patient on the basis of the findings of the preanesthetic visit.

As soon as the patient arrived in the operating room on the day of surgery, an intravenous infusion was started and blood pressure and ECG monitors were applied. Before performance of the lumbar puncture, 300–500 ml of crystalloid solution was administered to all patients, the exact volume depending on the size and physical status of the patient. Tetracaine was the anesthetic agent utilized in every case; regardless of whether Niphanoid crystals or the 1% solution was utilized, the tetracaine was always diluted to a final concentration of 0.5% with dextrose, spinal fluid, or distilled water, depending on the baricity desired. After administration of the spinal anesthetic, vasopressors were administered only if the systolic blood pressure decreased 20–30% below the preanesthetic value in spite of the administration of intravenous fluids.

The variables recorded in each case were classified as demographic, anesthetic, and surgical. The demographic variables included age, sex, and race. The

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Received from the Department of Anesthesiology, University of Illinois at Chicago, Chicago, Illinois. Accepted for publication April 27, 1988.

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anesthetic variables were subdivided into technical and pharmacologic categories as follows: Technical variables included the position of the patient during the administration of the spinal, the interspace utilized, the type of approach, the size of the needle, the number of attempts required to obtain cerebrospinal fluid, the color and flow characteristics of the spinal fluid before and after the injection of local anesthetic, whether paresthesias occurred during performance of the lumbar puncture, and the experience of the anesthetist. The pharmacologic variables included the form of tetracaine utilized; the dose, volume, and baricity; and the presence or absence of epinephrine in the local anesthetic solution. Surgical variables included the site of surgery and the duration of the surgical procedure.

The clinical efficacy of the spinal anesthetic was evaluated by recording the patient's subjective response to surgery and the necessity for supplemental agents to maintain patient comfort. For the purposes of this study a spinal anesthetic was classified as a failure if the surgical procedure could not be performed without the addition of general anesthesia, regardless of whether the failure was due to the absence of anesthesia, incomplete anesthesia, or complete anesthesia but with an inadequate level for the procedure. The need for intravenous supplementation with narcotics and/or tranquilizers alone was not considered a failure of spinal anesthesia provided these drugs were given in doses sufficient to keep the patient comfortable but responsive to verbal commands. A special data-retrieval form was filled out at the time of administration of each anesthetic, with data being analyzed using χ^2 and Fisher's exact tests as appropriate. $P \le 0.05$ was considered to be statistically significant.

Results

Using our criteria for failure, spinal anesthesia failed in eight of the 200 patients, an overall failure rate of 4%. The failures were analyzed in relation to each of the three variables as described below.

Demographic Variables

The study included 146 males and 54 females, 16–80 years old. Thirty percent of the patients were Caucasian, 19% were Hispanic, 47% were Black, and 4% did not fit into any of these categories. The rate of failure as related to each of the demographic variables is tabulated in Table 1, which indicates that the only variable causing a statistically significant difference was sex, with females having a higher failure rate than males. Although the failure rates were higher in Hispanics than in other ethnic groups, and higher in young patients than in older ones, these differences were not statistically significant.

Table 1. Failure Rate in Relation to Demographic Variables

Variable	Total number of spinal anesthetics	Successful spinal anesthetics	Failed spinal anesthetics	Failure rate (%)
Sex				
Male	146	144	2	1.4
Female	54	48	6	11.1*
Ethnic group				
White	60	59	1	1.7
Black	94	91	3	3.2
Hispanic	38	34	4	10.5
Other	8	8	0	0
Age (yrs)				
16–20†	2	2	0	0
20–40	59	55	4	6.8
40–60	55	53	2	3.6
60–80	84	82	2	2.4

*Difference highly significant ($P = 0.005$).
†Not included in statistical analysis, because number was too small.

Anesthetic Variables

Technical. The rate of failure as related to each of the technical variables is presented in Table 2. There was no significant difference in failure rates between spinal anesthetics administered in the lateral position (3.5%) and those administered in the sitting position (5.9%); and anesthesia was successful in all 15 patients in whom the anesthetic was administered and surgery carried out with the patient in the prone position. Surprisingly, the failure rate was higher when either the L3–4 (5.88%) or the L4–5 (7.31%) interspace was utilized as compared with the L2–3 or L5–S1 interspaces, neither of which was associated with failures. Most of the spinals (75%) were performed using a midline approach, with a failure rate of 5.63%. In the other 25% of the cases, either a paramedian approach or Taylor's approach was utilized, and there were no failures in any of these cases. Neither needle size nor number of attempts at lumbar puncture significantly influenced the failure rate. Traumatic subarachnoid puncture (bloody tap) was encountered in six patients, but all of these patients had adequate anesthesia. Free flow of CSF was demonstrated before injection in all cases in whom the

Table 2. Failure Rate in Relation to Technical Variables

Variable	Total number of spinal anesthetics	Successful spinal anesthetics	Failed spinal anesthetics	Failure rate (%)
Position				
Lateral	113	109	4	3.5
Sitting	72	68	4	5.9
Prone	15	15	0	0
Interspace				
L2–3	56	56	0	0
L3–4	85	80	5	5.9
L4–5	44	41	3	7.3
L5–S1	15	15	0	0
Approach				
Midline	150	142	8	5.6
Paramedian	35	35	0	0
Taylor's	15	15	0	0
Needle size				
18-gauge	19	18	1	5.3
22-gauge	104	100	4	3.8
25-gauge	77	74	3	3.9
Number of attempts				
1	130	129	1	0.8
2	39	34	5	10.3
3	13	12	1	7.7
4	7	7	0	0
>5	10	10	1	10
CSF				
Clear	193	186	7	3.6
Bloody	6	6	0	0
CSF flow*				
Free flow (preinjection)	198	192	6	2.5
Free flow (postinjection)	196	192	0	0
Level of training				
PGY-2	157	152	5	3.2
PGY-3	19	17	2	10.5
PGY-4	17	16	1	5.9
Attending	7	7	0	0

*Free flow was demonstrated before injection in all cases except two technical failures where the subarachnoid space could not be identified. Free flow after injection was not obtained in two cases, both of which had successful spinal anesthesia. There were no statistically significant differences with respect to the different technical variables.

subarachnoid space was identified (198 cases), and 6 of these 198 cases had failed spinals. In two patients, free CSF flow was not obtained after injection, and both these patients had successful spinals. Finally, with respect to the influence of the level of training of the anesthetist on failure, PGY-3 residents had a higher failure rate than either the PGY-4 or PGY-2 residents, but these differences were not significantly different.

Pharmacologic. The rate of failure as related to the pharmacologic variables is tabulated in Table 3. The anesthetic preparation that resulted in the highest failure rate (16.6%) was the 1% solution of tetracaine diluted to 0.5% with 5% dextrose with epinephrine 1:10,000. Interestingly, the 1% solution without epinephrine provided the highest success rate, i.e., no failures! However, if all the patients who received tetracaine with epinephrine are considered as a group (i.e., without respect to whether it was prepared from crystals or solution), the overall failure rate with epinephrine was 5% and that without epinephrine was 3.3%, a difference that was not significant. Hyperbaric solutions were used in 80% of the patients, with a failure rate of 4.34%; isobaric solutions were used in 12.5% of the cases with no failures; and hypobaric solutions were used in the remaining 7.5%, also with no failures.

Surgical Variables

The rate of failure as related to the surgical variables is presented in Table 4. Note that "duration of sur-

Table 3. Failure Rate in Relation to Pharmacologic Variables

Variable	Total number of spinal anesthetics	Successful spinal anesthetics	Failed spinal anesthetics	Failure rate (%)
Drug preparation*				
Niphanoid tetracaine	80	77	3	3.8
Niphanoid with epinephrine	62	61	1	1.6
1% Tetracaine solution	40	40	0	0
1% Solution with epinephrine	18	15	3	16.6†
Baricity				
Hypobaric	15	15	0	0
Hyperbaric	160	152	7	4.3
Isobaric	25	25	0	0

*Irrespective of tetracaine preparation the overall failure rate was 5% with epinephrine and 3.3% without epinephrine, a difference that was not significant.
†Difference significant ($P < 0.02$).

Table 4. Failure Rate in Relation to Surgical Variables

Surgical site	Total number of spinal anesthetics	Successful spinal anesthetics	Failed spinal anesthetics	Failure rate (%)
Abdominal				
Intraperitoneal				
Appendectomy, laparoscopy	10	8	2	20.0
Extraperitoneal				
Hernia	10	9	1	10.0
Lower extremity	67	64	3	4.5
Genitourinary	76	74	1	1.3*
Perineal				
Hemorrhoids, rectal abscess, fissure, etc.	32	32	0	0*
Gynecologic†	4	4	0	0

*Difference statistically significant compared to intraperitoneal abdominal; ($P < 0.05$).
†Number too small for statistical comparison.

gery" is not listed as a variable related to failure, because in none of the 200 cases did the duration of surgery exceed the duration of anesthesia, so failure was never due to inadequate duration. As one might expect, there is a direct relation between the failure rate of spinal anesthesia and the level of surgery. Thus, a higher number of failures occurred when spinal anesthesia was used for intraperitoneal (most of which were upper abdominal) (20%) as compared with extraperitoneal (most of which were lower abdominal) (10%) procedures; and, similarly, there was a higher number of failures when spinal anesthesia was used for lower abdominal as compared with genitourinary (1.3%), perineal (0%), and lower extremity surgery (4.5%). Interestingly, of the 67% of the cases where spinal anesthesia was used for lower extremity surgery, none of the three failures was caused by tourniquet pain. And finally, and perhaps most importantly, there were no serious complications and/or sequelae in any of the cases.

Discussion

The purpose of the present study was to determine the rate of spinal anesthesia failure at our institution, to compare that rate with those published by other institutions and, by analyzing the factors contributing to failure, to determine, if possible, the reasons for the differences between our failure rate and the rates in other institutions. However, it is difficult to compare our data with those from other institutions because 1) the criteria for success and failure differ from study to study; 2) our study is prospective whereas most others are retrospective with respect to data collection; and 3) in many studies of spinal anesthesia the failure rate and the factors contributing to it are not the primary objectives of the study (Table 5).

Therefore, we attempted to eliminate the first two of these differences in the present study by employing criteria similar to those used by Levy (1) and

Table 5. Previously Reported Spinal Failure Rates

Study	Year	Type of study	Failure rate percentage
Moore et al. (3)	1968	Retrospective	0.46
Moore (4)	1980	Prospective	14–16
Moore (5)	1982	Prospective	10.6
Bridenbaugh (6)	1982	Prospective	5
Smith et al. (7)	1986	Prospective*	5% with epinephrine; 35% without
Levy et al. (1)	1985	Retrospective*	17
Manchikanti et al. (2)	1987	Retrospective*	3

*Study designed specifically to look at failure rates.

Table 6. Factors Affecting Success or Failure of Spinal Anesthesia

Technical factors
1. Identification of subarachnoid space; related to training; ability to utilize different approaches
2. Documentation of free flow of CSF pre- and postinjection
3. Proper placement of catheter for continuous spinal technique

Pharmacologic factors (judgment error)
1. Selection of appropriate local anesthetic and addition of vasoconstrictor; depending on duration of surgery
2. Selection of appropriate dosage and baricity
3. Selection of appropriate position and interspace; depending on site of surgery
4. Selection of appropriate technique; single injection versus continuous catheter technique

Manchikanti (2) and their associates, because these are the only two studies in which the primary objective was to determine the spinal failure rate. However, a major difference between our study and theirs remains: Ours was prospective, theirs retrospective with respect to data collection. In any case, our failure rate was only 25% of that reported by Levy et al. (17%) and 50% of that reported by Manchikanti et al. (8.8%). (Although the overall failure rate reported by the latter authors was 3%, the failure rate when tetracaine was used as a local anesthetic was 8.8%.) These differences are even more impressive when one realizes that the study by Levy et al. considered only the need for general anesthesia as a failure and regarded situations in which "pain persisting throughout the procedure despite the frequent administration of narcotics or tranquilizers or both" as successful spinals. These cases would have been classified as failures both in Manchikanti's study and in ours. Other studies that have included spinal failure rate in their data have reported extremely variable results, with failure rates as low as 0.46% and as high as 35% (1–7). Undoubtedly, the reasons for such enormously dissimilar results are the three difficulties to which we have already alluded that prevent comparison of such data between many studies. Thus, we have limited our comparisons to the two studies in which two of the three difficulties do not pertain.

Although the demographic factors have a definite impact on spinal failures and are of interest, in terms of analyzing factors that can be corrected and/or controlled to reduce the rate of failure it is the anesthetic variables that are of greatest interest. Furthermore, just as the anesthesiologist needs technical dexterity to control the technical factors, he or she needs judgment to utilize the anesthetic properly (proper dose, volume, baricity). Thus, in discussing the causes of failure, we have divided the failures etiologically into two groups: those due to technical errors and those due to errors in judgment (Table 6). It is important to note that errors in technique usually resulted in *complete* failure, i.e., no block or patchy block, whereas errors in judgment resulted in partial failures, i.e., inadequate level, inadequate duration, inadequate relaxation, etc. In this study, only 25% of the failures (two patients) were due to technical factors: in one patient the subarachnoid space could not be identified; and in the other, improper catheter placement resulted in failure of a continuous spinal technique. Although the numbers are too small to establish statistical significance in this study, in the study by Levy et al., inability to identify the subarachnoid space and/or lack of free flow of CSF before injection was the most common cause of failure due to technical factors. We failed to find any correlation between free flow of CSF and success and/or failure. In fact, inability to obtain free flow of CSF *following* injection usually indicates movement of the spinal needle out of the subarachnoid space *during* the injection and implies a greater chance of failure or partial block. Yet failures did not result in our study even when this occurred.

Although success with spinal anesthesia is related in large part to an understanding of the anatomy involved in lumbar puncture, perhaps even more important is clinical experience with the technique. The former can be obtained didactically at all institutions, but the latter will vary from institution to institution. Furthermore, experience with alternative approaches, i.e., paramedian, lateral, and Taylor's approach, can lead to successful identification of the subarachnoid space when the midline approach is difficult or impossible. The extensive clinical experience with spinal anesthesia at our institution is probably the reason for the low failure rate due to technical factors (1% of all the cases).

However, technical dexterity is easier to acquire than is clinical judgment, and errors in judgment, which tend to involve primarily pharmacologic factors, were the most common cause of failure in our study, constituting 75% (six patients) of all the failures. As can be seen in Table 4, surgical procedures involving intraperitoneal manipulations accounted for 20% of the failures secondary to an inadequate level of surgical anesthesia. Clearly, in these cases the main reason for failure was the inability of the anesthetist to obtain a level of anesthesia adequate to block the splanchnic nerves and thus provide anesthesia of the abdominal peritoneum, usually because of improper positioning and/or an inappropriate level of injection. Our data corroborate the observation of Lee et al. (8) that the failure rate in patients undergoing abdominal surgery is higher in cases in which lumbar puncture was performed below the summit of the lumbar convexity. Injection below this point results in preferential flow of a hyperbaric solution toward the sacral concavity unless the patient is positioned in such a way that the lumbar lordosis is either removed or diminished or unless the table is tilted with the head down far enough to assure that hyperbaric solutions surmount the lumbar lordosis and reach the thoracic concavity.

The significantly greater number of failed spinals (16.6%) when epinephrine was added to the tetracaine solution was an unexpected finding and is contrary to the findings of Levy (1) and Smith (7) and their associates. On the other hand, the findings of Manchikanti et al. (2) were similar to ours in that the addition of epinephrine almost tripled their failure rate and, like us, they could not explain this finding. However, the difference in our study may be more apparent than real if the type of tetracaine preparation is not taken into account: the overall failure rate in the tetracaine (Niphanoid and liquid) with epinephrine group was 5%, and that in the tetracaine (Niphanoid and liquid) without epinephrine group was 3.3%, a difference that is not significant (Table 3).

In previous studies demographic factors were not considered as factors related to spinal failure. Interestingly, we found a higher failure rate in Hispanic patients than in other ethnic groups and, in addition, a failure rate higher in females than in males. The higher failure rate in Hispanics, especially in females, is undoubtedly related to the importance communication plays in allaying anxiety and allowing cooperation, both of which are important to patient acceptance and to the ultimate success of regional anesthesia. There appeared also to be an inverse relation between patient age and spinal failure. The lower failure rates in older patients may be related to the slower absorption of local anesthetic, resulting in a more intense block and a longer duration of anesthesia.

In summary, the present study indicates that at our institution, a university teaching hospital, it is primarily errors in judgment with respect to pharmacologic factors, i.e., choice of drug, dose, and baricity, and proper positioning of the patient, that most commonly result in an unsatisfactory level and/or duration of block and spinal failure. Only with experience gained under the guidance of skilled teachers can the neophyte anesthesiologist develop not only the technical skills but, more important, the clinical judgment that results in a low incidence of failed spinals. Bridenbaugh (9) recently reported the results of a survey of residency programs and the degree to which they are teaching regional anesthesia and concluded that many anesthesiology residency programs are failing to teach regional anesthesia. Without this experience it is no wonder that the failure rates of spinal anesthesia (and other regional technique) are high and, of course, with such high failure rates anesthesiologists are reluctant to use spinal anesthesia even when indicated. We believe that the low incidence of failed spinals in our study is related to the extensive clinical experience in regional anesthesia gained by residents at our institution.

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ANESTH ANALG 849
1988;67:849–51

The Immunologic Profile of Anesthetists

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ZIV Y, SHOHAT B, BANIEL J, VENTURA E, LEVY E, DINTSMAN M. The immunological profile of anesthetists. Anesth Analg 1988;67:849–51.

Reports in the literature have suggested possible impairment of immunocompetence in operating theater personnel. In a group of 18 physician anesthesiologists the following were determined: hemoglobin concentration; white blood cell count; numbers of T, B, and natural killer (NK) lymphocytes; number of T-active cells; and numbers of T-helper/inducer (Th) and T-suppressor/cytotoxic (Ts) cells; and the Th/Ts ratio. Function of T lymphocytes was evaluated using the local xenogeneic graft-versus-host reaction and spontaneous suppressor or helper activity of T cells. The same parameters were determined in a group of 18 age- and sex-matched healthy controls. It was found that no matter what their age or how long they have been engaged in anesthetic practice, anesthetists show no immunosuppression as evidenced by these parameters.

Key Words: IMMUNE RESPONSE—immunocompetence of anesthetists. ANESTHESIOLOGISTS—immunocompetence.

Evidence has been presented to suggest that anesthetists may suffer suppression of some immunologic function. Volatile anesthetics have been shown to be toxic to lymphocytes at anesthetic concentrations in vivo and in vitro (1). Pettingale et al. (2) reported immunosuppression among anesthetists, but others (3,4) failed to demonstrate any reduced immunocompetence in operating room personnel. Mathieu et al. (5) found the data in the literature as to whether T-lymphocyte function is altered in anesthetists and other operating room personnel to be conflicting.

We studied the immunologic profile of 18 anesthetists as well as 18 age- and sex-matched healthy controls in an attempt to resolve the inconsistencies reported in previous studies of immunological status of anesthetists.

Materials and Methods

Subjects included 18 physician anesthesiologists (14 males and 4 females aged 30–57 years old) regularly working in the operating room for 2–30 years (mean 9.1). The approximate percentage use of volatile agents, narcotic techniques, and regional anesthesia was 45, 45, and 10%, respectively. None of the anesthetists were taking any medication causing immunosuppression, and none had been on vacation during the preceding 2 months. Eighteen age- and sex-matched subjects in good general health who were hospitalized for repair of an inguinal hernia, had had no occupational exposure to toxic nonanesthetic agents, and were not employed in hospitals, served as controls. In all subjects the following were determined: hemoglobin concentration; white blood cell count; numbers of T, B, and natural killer (NK) lymphocytes; numbers of T-active cells, T-helper/inducer (Th) cells, and T-suppressor/cytotoxic (Ts) cells; and the Th/Ts ratio.

Fresh venous blood obtained at 8 AM was drawn into heparinized syringes, and lymphocytes were separated on Ficol-Hypaque gradient (LSM). Cells were washed three times in phosphate-buffered saline (PBS) and resuspended in RPMI-1640 medium with 10% fetal calf serum (FCS). Total T lymphocytes were determined by rosetting nonadherent cells with sheep erythrocytes at 4°C for at least 1 hour. T-active cells were determined by rosetting nonadherent cells with sheep erythrocytes after 1 hour of incubation with FCS at 37°C. T-lymphocyte subpopulations were quantitated by indirect immunofluorescence using fluorescein-conjugated monoclonal antibodies OKT-4

Received from the Department of Surgery "A," the Cellular Immunology Unit, and the Department of Anesthesiology, Beilinson Medical Center, Petah Tikva, and the Sackler School of Medicine, Tel Aviv University, Israel. Accepted for publication April 28, 1988.

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Table 1. Comparison of Immunologic Profiles of a Group of 18 Anesthetists and a Group of Matched Controls

	Anesthetists (n = 18) (mean ± SD)	Controls (n = 18) (mean ± SD)	P*
Age (yrs)	40.2 ± 7.1	38.9 ± 6.4	NS
Male/female ratio	14/4	14/4	
Hemoglobin (wt %)	14.18 ± 3.61	14.27 ± 2.92	NS
White blood cells/mm^3	7261 ± 1221	6429 ± 1240	NS
Lymphocytes (%)	32.35 ± 5.72	32.49 ± 7.56	NS
Total lymphocytes/mm^3	2317 ± 418	2151 ± 511	NS
T cells/mm^3	1796 ± 377	1685 ± 405	NS
T-active cells/mm^3	904 ± 262	856 ± 300	NS
B cells/mm^3	228 ± 87	224 ± 97	NS
T-helper (Th)/inducer cells · mm^3	961 ± 283	821 ± 200	NS
T-suppressor (Ts)/cytotoxic cells/mm^3	600 ± 240	512 ± 230	NS
Ratio Th/Ts	1.80 ± 0.79	1.92 ± 0.83	NS
Natural killer cells/mm^3†	247 ± 98	221 ± 75	NS
GVHR‡	Positive 17/18	Positive 16/18	NS
SSA (%)§	25.69 ± 34.81	22.48 ± 45.37	NS

*Results of two-sample Student's t-test; NS = not significant.
†13 anesthetists examined.
‡GVHR = graft-versus-host reaction.
§SSA = Spontaneous suppressor activity; percent of inhibition or enhancement of GVHR.

and OKT-8 specific for Th and Ts lymphocytes, respectively, and Leu-11B monoclonal antibody specific for NK cells. B-lymphocytes were quantitated by direct immunofluorescence using the membrane immunoglobulin SIg and counted by fluorescence microscopy.

Function of T lymphocytes was evaluated using the local xenogeneic graft-versus-host reaction (GVHR), and spontaneous suppressor or helper activity of T-cells (SSA) was determined by adding the subject's T lymphocytes to normal lymphocytes from the blood bank in the GVHR procedure and comparing the size of the reaction induced by the normal donor lymphocytes to that induced by normal donor lymphocytes with the patient's lymphocytes. The investigators were unaware of whether samples were from the anesthetists or from the control subjects. The two-sample Student's t-test was used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results

Comparison of the immunologic profile of the 18 anesthetists who had been working in an operating room for varying periods of time with that of a healthy control group revealed no statistically significant differences between the two groups. The means and standard deviation of the various data are presented in Table 1.

Discussion

In their review on the occupational hazards of anesthesia, Vessey and Nunn (6) suggested that operating room nurses or female anesthetists who have become pregnant or wish to become pregnant should be advised to avoid working in an environment contaminated with anesthetic gases, such as operating theaters without effective scavenging systems. In recent reports, alterations in the number and function of circulating lymphocyte subpopulations have been implicated in abnormal immune responses observed in a variety of diseases (7). However, studies on peripheral blood T and B lymphocytes in operating room personnel have yielded conflicting results. Our findings support those of Salo and Vapaavuori (4), who found no statistical difference between operating theater personnel and controls in regard to numbers of T and B lymphocytes determined by the rosette and surface immunoglobulin (SIg) methods.

Duncan and Cullen (1) and Bruce (8) found that halothane in clinical or higher concentrations had immunosuppressive effects that they considered representative of similar effects of all potent volatile anesthetics. Bruce (8) found that halothane prevents resting cells from entering the cell cycle when signalled to do so. However, in another study on a small number of subjects within a restricted age range, Bruce (3) reported that he found no support for the hypothesis that occupational exposure to anesthetics causes immunosuppression among anesthetists.

Nitrous oxide has been said to be capable of affecting the immunologic response. The noxious effects of long-term exposure to anesthetic concentrations of nitrous oxide on the bone marrow of animals and humans are well known (5). In rats, nitrous oxide decreases the number of antibody-producing cells in the spleen and has a tendency to reduce serum antibody titers when administered in concentrations of 75% (9). Other factors in operating rooms that may cause a change in the immune response include stress and emotional distress (10).

Previous studies have indicated that the "active" rosette-forming cells represent a reliable index of cell-mediated immune function, whereas the total number of rosette-forming cells, or total T, reflects the presence and distribution of T cells without necessarily indicating their functional ability (4). Mathieu et al. (5) found an increase in "active" T cells and a decreased polymorphonuclear count in operating room personnel, suggesting increased T-cell activity. In our study we found a normal number of "active" T cells and no decrease in the white blood count. Pettingale et al. (2) reported a significant reduction in the total lymphocyte count, T cells, and phytohemagglutinin (PHA) transformation in anesthetists. They found no relation between the reduction in total lymphocyte count and either age or time engaged in anesthetic practice, but concluded that immunocompetence in anesthetists may not be normal. This is in contrast with our finding that no matter what their age or how long they have been engaged in anesthetic practice, anesthetists show no immunosuppression as evidenced by the lymphocyte count, B- and T-cell subpopulations, natural killer cells, and T-lymphocyte function.

We thank R. Koren, I. Levy, and D. Koflick of the Cellular Immunology Unit for invaluable technical assistance.

This article is dedicated to the recently deceased E. Ventura, MD, who served as Deputy Chief of the Department of Anesthesiology.

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Differential Effects of Isoflurane/Nitrous Oxide on Posterior Tibial Somatosensory Evoked Responses of Cortical and Subcortical Origin

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WOLFE DE, DRUMMOND JC. Differential effects of isoflurane/nitrous oxide on posterior tibial somatosensory evoked responses of cortical and subcortical origin. Anesth Analg 1988;67:852–9.

Posterior tibial somatosensory evoked responses (SSERs) were recorded during administration of isoflurane and nitrous oxide. Responses arising from cortical and subcortical neural generators were examined to compare their relative resistance to anesthetic-related degradation. Recordings were performed in ten adults during anesthesia with 0.5 MAC isoflurane/60% N_2O, 1.0 MAC isoflurane/60% N_2O, and 1.5 MAC isoflurane/60% N_2O. Thereafter, N_2O was omitted and recordings were repeated during anesthesia with 1.5 and 1.0 MAC isoflurane/O_2. Isoflurane resulted in a significant ($P < 0.001$) dose-related decrease in the amplitude of cortical waveforms. The amplitude loss was substantial; e.g., for the first cortical waveform, amplitude decreased from 1.21 ± 0.67 μV during 0.5 MAC isoflurane/N_2O to 0.28 ± 0.29 μV during 1.5 MAC/N_2O. Elimination of N_2O resulted in an increase in amplitude of approximately 100% ($P < 0.04$). By contrast, the amplitude of the subcortical response as recorded in vertex to linked mastoid and vertex to upper cervical spine derivations was not significantly altered by changing concentrations of isoflurane or N_2O. The results suggest that subcortical SSERs may be preferable to those of cortical origin for spinal cord monitoring in situations where isoflurane and nitrous oxide, especially in varying concentrations, are the primary anesthetic agents.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANESTHETICS, GASES—nitrous oxide. MONITORING, EVOKED RESPONSES—somatosensory. BRAIN, EVOKED RESPONSES—somatosensory.

It has been well documented that anesthetics, particularly volatile anesthetics, alter somatosensory evoked responses (1–8). Numerous authors have emphasized the need to maintain constant anesthetic levels during evoked response monitoring, and some have even advocated the complete avoidance of volatile anesthetic agents when SSERs are recorded (9). Many reports of intraoperative monitoring of evoked responses to lower extremity stimulation (3–5,10–13) have emphasized the use of scalp–scalp electrode montages, e.g., Cz'–FPz, from which responses of cortical origin are recorded. However, it has been noted that waveforms generated at cortical sites are the most sensitive to the effects of anesthetic agents and that responses arising from spinal or subcortical generators are generally more resistant (6,7,14,15). Spinal responses are not always an attractive monitoring alternative because amplitude diminishes at upper spinal cord levels (15–18), and over the cervical spine they may be of very low amplitude and difficult to record expediently in the "noisy" operating room environment. However, a more readily recorded far-field response of subcortical origin (medial lemniscus or thalamus) can be recorded between electrodes placed at the vertex and the cervical spine (e.g., Cz'–C2S) or the vertex and the mastoid processes. This response appears to be more resistant to anesthetic influence, and some reports describe its use in intraoperative spinal cord monitoring (4,15). However, the relative vulnerability to the effects of anesthetic agents of cortical and subcortical responses recorded in these various montages has never been examined systematically. The present study was undertaken to compare the effects of isoflurane and nitrous oxide on these responses in humans.

Received from the Department of Anesthesiology of the Veterans' Administration Medical Center, La Jolla, California; the Department of Anesthesiology, University of California, San Diego; and the Department of Anesthesiology, U.S. Naval Hospital, San Diego, California. Accepted for publication April 29, 1988.

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Methods

The protocol was approved by the Human Subjects Committees of the University of California at San Diego and the Veterans Administration Medical Center, La Jolla, California. Informed consent was obtained from 13 patients. Each patient was scheduled to undergo an elective surgical procedure for which an isoflurane/nitrous oxide anesthetic was deemed appropriate. Patients undergoing neurosurgical, spinal, and aortic procedures were excluded. No patient was receiving chronic CNS-active medications, and all were free of neurologic disease. Premedication was administered at the discretion of the attending anesthesiologist.

A bar electrode stimulator (interelectrode distance 3 cm) was used to locate the posterior tibial nerve adjacent to the medial malleolus at the ankle. The identified sites were marked, and platinum needle electrodes (Grass) were inserted perpendicularly. The cathode was placed proximal. Gold disk recording electrodes (Grass) were positioned in accordance with the International 10–20 system to create four montages as follows:

Cz′–FPz (Cz′ is 2 cm posterior to Cz)
Cz′–C2S (second cervical spinous process)
Cz′–LM (linked mastoid processes)
FPz–C2S

The ground electrode was placed over the middle third of the left clavicle. Recording electrode impedances were maintained at ≤3 kohm. Stimulation and recording were performed with a Tracor Northern Nomad (Madison, Wisconsin). Stimulus intensity was adjusted to two times motor threshold. For each SSER, 250 constant-current impulses of 100-μsec duration delivered at a rate of 3.1 Hz were averaged. A time base of 110 msec after stimulus was analyzed. The low and high filters were set at 30 and 750 Hz, respectively. The acquired signals were amplified 100,000 times (corresponding to a Nomad sensitivity setting of 50 μV). Averages were performed in duplicate and examined for reproducibility (see Fig. 1), and a grand average of 500 repetitions was produced by adding the individual waveforms. All waveforms were recorded on magnetic disk and on paper. The initial positive deflection (approximate latency 30–34 msec) in each montage was labeled P0, and the following negativity N0. The succeeding positive deflections were labeled P1 and P2, with the following negativities designated N1 and N2. In general, the P0-N0 complex was not evident in the Cz′–FPz montage, and the first apparent waveform in this montage was commonly P1. Latencies and amplitudes were determined with electronic cursors. Amplitude was measured from the positive peak to the subsequent negativity. Brief trials of SSER recording were commonly performed preceding induction as a verification of the function of the recording system. Systematic collection of data began after induction of anesthesia. One or both posterior tibial nerves were stimulated as dictated by surgical circumstances. In all cases, the same investigator (DEW) supervised the administration of the anesthetic and performed the SSER analysis using the same apparatus and technique.

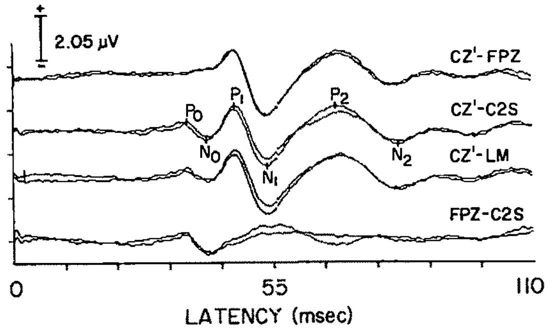

Figure 1. Somatosensory evoked responses to posterior tibial nerve stimulation recorded simultaneously from four electrode montages in a patient anesthetized with 0.5 MAC isoflurane/60% nitrous oxide. The nomenclature used to identify waveforms is indicated on the responses recorded in the Cz′–C2S montage.

Anesthesia was induced with thiopental 4–6 mg/kg IV. Succinylcholine was administered to facilitate intubation of the trachea. Immediately after intubation, isoflurane in 60% nitrous oxide/balance oxygen was introduced in a total fresh gas flow of 5 L/min. Overpressure was employed to bring the end-tidal isoflurane concentration to 0.5 MAC. (In this paper, the term MAC is used to identify the end-tidal concentration of isoflurane without allowance for the anesthetic contribution of any simultaneously administered nitrous oxide. All MAC values were age-adjusted [19].)

An end-tidal isoflurane concentration of 0.5 MAC was maintained for 15 minutes, and the initial duplicate SSER determinations were performed. The end-tidal concentration was then increased to 1.0 MAC and then to 1.5 MAC. At each level, a constant end-tidal concentration was maintained for 15 minutes before beginning data acquisition. After data collection during administration of 1.5 MAC isoflurane/60% nitrous oxide, the nitrous oxide was omitted and replaced with oxygen. Fifteen minutes was allowed for nitrous oxide elimination, and duplicate SSER recordings were repeated. When consistent with the prevailing anesthetic requirements, the isoflurane concentration was reduced to 1.0 MAC (in

Table 1. Physiologic Variables during Anesthesia with Isoflurane (I) and nItrous Oxide

	MAP	HR	Temp	$ETco_2$
0.5 MAC I/60% N_2O	98 ± 9	87 ± 13	35.7 ± 0.6	37 ± 4
1.0 MAC I/60% N_2O	88 ± 14	84 ± 18	35.5 ± 0.5	37 ± 3
1.5 MAC I/60% N_2O	79 ± 11	87 ± 13	35.4 ± 0.7	35 ± 3
1.5 MAC I/O_2	80 ± 14	85 ± 12	35.5 ± 0.7	35 ± 5
1.0 MAC I/O_2	92 ± 14	83 ± 12	35.4 ± 0.6	35 ± 4

All values are expressed as mean ± SD.
MAP, mean arterial pressure, mm Hg; HR, heart rate, beats/min; Temp, esophageal temperature, °C; $ETco_2$, end-tidal carbon dioxide concentration, mm Hg.

100% oxygen) and the fifth and final duplicate SSER recordings were performed.

Throughout the study, ventilatory parameters were adjusted to maintain an end-tidal carbon dioxide concentration (Saracap or Hewlett-Packard capnographs) of 30–40 mm Hg. Patient temperature was monitored with an esophageal thermistor. Isoflurane concentration in gas sampled at the endotracheal tube connector was measured with a Puritan-Bennett Anesthetic Agent Monitor 222 (sampling rate approximately 200 ml/min). The 0.5 MAC/60% N_2O determination was made before the surgical incision, with the remainder of the responses recorded thereafter. On occasion, ephedrine in 5-mg increments was administered to maintain systolic arterial blood pressure above 90 mm Hg. Neuromuscular relaxants were administered according to the requirements of the surgical situation, but no other anesthetic agents or adjuvants were administered during the period of study.

Statistical Analysis

The changes in latencies and amplitudes that occurred with increasing concentrations of isoflurane were examined using a repeated measures analysis of variance. Where a significant change was identified, pairwise comparisons were performed using a Bonferroni corrected Student's *t*-test for paired data to identify the isoflurane concentration at which significant ($P < 0.05$) differences from baseline (0.5 MAC/60% nitrous oxide) first occurred. The influence of nitrous oxide was examined using paired *t*-tests to compare latencies and amplitudes observed with and without 60% N_2O during administration of both 1.0 MAC and 1.5 MAC isoflurane.

Results

Of the 13 patients who consented to participate, three were excluded—one because of difficulty with intubation resulting in the administration of thiopental in excess of 15 mg/kg; one because of relative hypothermia (esophageal temperature 34.5°C) at the time of the first intended data collection; and one because of contamination of the cranial-cervical derivation by muscle artifact. Of the ten remaining patients, there were nine males and one female. The mean age was 43 ± 12 (SD) years (range 26–65), and the mean height was 178 ± 5 cm. Three of the subjects received no premedication; four received IM midazolam 1–5 mg; and three received oral diazepam 5 mg. The minimum interval between premedication and the first evoked response determination was 90 minutes.

In two of the ten subjects, the 1.5 MAC determinations were omitted as a result of cardiovascular intolerance. Two subjects required ephedrine during the course of the study to maintain systolic blood pressure above 90 mm Hg; however, in neither instance did the total dose of ephedrine exceed 20 mg.

The mean arterial pressure, heart rate, temperature, and end-tidal carbon dioxide data are provided in Table 1. Note that in spite of efforts to maintain body temperature, a moderate reduction (to 35.7 ± 0.6°C) consistently occurred during the period of induction, positioning, and skin preparation that preceded the initial data acquisition. Temperature remained constant thereafter.

Latency (P0, P1, P2) and amplitude P0-N0, P1-N1, P2-N2) data for waveforms recorded in each of the four montages are presented in Table 2. Note that the P0-N0 complex was not evident in the Cz'–FPz montage, and accordingly no data are provided for P0 latency or P0-N0 amplitude in this lead. In the FPz–C2S montage, only the P0-N0 waveform was consistently recordable. For this lead the only data are for the latency of P0 and the amplitude of P0-N0.

The addition of each 0.5 MAC increment of isoflurane to the baseline anesthetic condition (0.5 MAC isoflurane/60% N_2O) resulted in a decrease in the amplitudes ($P < 0.001$) of the cortically generated waveforms (P1-N1, P2-N2) in the three montages in which they were recordable (Table 2, Fig. 2). In all

Table 2. Amplitudes (μV) and latencies (msec) of Posterior Tibial Somatosensory Evoked Responses during Anesthesia with Isoflurane/N_2O and Isoflurane/O_2

	0.5 MAC/N_2O (n = 10)	1.0 MAC/N_2O (n = 10)	1.5 MAC/N_2O (n = 8)	1.5 MAC/O_2 (n = 8)	1.0 MAC/O_2 (n = 10)
Amplitudes					
PO-NO					
Cz'–C2S	0.50 ± 0.19	0.53 ± 0.23	0.48 ± 0.22	0.47 ± 0.21	0.50 ± 0.20
Cz'–LM	0.39 ± 0.18	0.40 ± 0.17	0.39 ± 0.15	0.35 ± 0.16	0.37 ± 0.16
FPz-C2S	0.58 ± 0.22	0.57 ± 0.26	0.55 ± 0.22	0.49 ± 0.25	0.48 ± 0.25
P1-N1					
Cz'-FPz	1.21 ± 0.67	0.63 ± 0.55*	0.28 ± 0.29	0.67 ± 0.53†	1.27 ± 0.79
Cz'-C2S	0.98 ± 0.64	0.60 ± 0.36*	0.26 ± 0.22	0.66 ± 0.42†	1.00 ± 0.67
Cz'-LM	1.05 ± 0.66	0.62 ± 0.39*	0.30 ± 0.24	0.69 ± 0.41†	1.08 ± 0.73
P2-N2					
Cz'-FPz	1.02 ± 0.66	0.44 ± 0.41*	0.18 ± 0.22	0.41 ± 0.34†	0.73 ± 0.44
Cz'-C2S	0.97 ± 0.67	0.44 ± 0.39*	0.19 ± 0.25	0.40 ± 0.37	0.75 ± 0.41
Cz'-LM	0.99 ± 0.70	0.43 ± 0.37*	0.18 ± 0.22	0.42 ± 0.30†	0.75 ± 0.41
Latencies					
P0					
Cz'-C2S	34.2 ± 2.2	34.4 ± 1.9	35.0 ± 1.9	35.4 ± 2.1	35.1 ± 1.8
Cz'-LM	34.2 ± 2.1	34.3 ± 1.8	34.9 ± 1.9	35.4 ± 2.1	35.3 ± 2.0
FPz-C2S	34.0 ± 1.9	34.2 ± 1.7	34.7 ± 1.9*	35.2 ± 1.9	34.7 ± 1.7
P1					
Cz'-FPz	44.2 ± 3.8	45.1 ± 3.8 (9)	45.5 ± 2.5* (6)	46.1 ± 2.1	45.5 ± 2.8
Cz'-C2S	44.5 ± 3.7	45.2 ± 3.3	47.3 ± 5.3 (6)	46.4 ± 2.0	46.1 ± 2.4
Cz'-LM	44.4 ± 3.7	45.0 ± 3.2	46.8 ± 5.0 (6)	46.3 ± 2.0	46.1 ± 2.7
P2					
Cz'-FPz	65.7 ± 4.3	65.5 ± 3.0 (8)	65.7 ± 4.0 (5)	67.9 ± 3.3 (7)	68.8 ± 2.9
Cz'-C2S	65.4 ± 5.7	69.3 ± 9.9 (9)	61.6 ± 3.1 (4)	67.4 ± 3.7 (7)	67.9 ± 3.6
Cz'-LM	65.4 ± 5.6	69.1 ± 10.0 (9)	62.2 ± 3.1 (4)	70.2 ± 7.5	69.2 ± 3.3

Values are mean ± SD. n = number of subjects at each anesthetic level. Where latencies were indeterminate because of absent waveforms, the reduced n is given in parentheses.

*Level at which significant ($P < 0.05$) difference from baseline (0.5 MAC/N_2O) first occurred.

†In these cases there was a significant difference between 1.5 MAC/N_2O and 1.5 MAC/O_2.

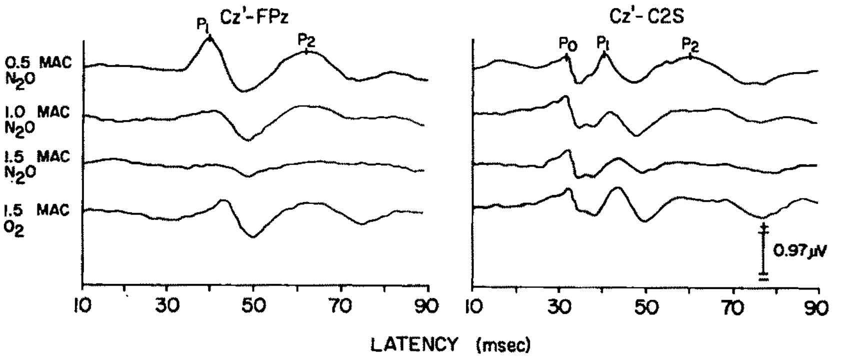

Figure 2. Posterior tibial SSERs recorded simultaneously in the Cz'–FPz and Cz'–C2S montages during anesthesia with isoflurane/N_2O and isoflurane/O_2. Note the progressive decrease in the amplitudes of the cortically generated waveforms (P1-N2, P2-N2) with increasing concentrations of isoflurane and the recovery of amplitude after withdrawal of N_2O. Note also the relative resistance of the amplitude of the subcortical waveform (P0-N0) to anesthetic effect.

instances, the decreases in the amplitude of the cortical waveforms were statistically significant at the 1.0 MAC/60% N_2O level (i.e., after the first 0.5 MAC isoflurane increment). The changes were substantial. For instance, during 1.0 MAC/60% N_2O and 1.5 MAC/60% N_2O anesthesia, the average amplitude of the P1-N1 complex in the Cz'–FPz derivation decreased to 52% and 23% of baseline, respectively (Table 2). In a small number of subjects, P1-N1 and P2-N2 became unidentifiable at the higher isoflurane concentrations (Table 2).

Variation of the inspired concentrations of isoflurane and nitrous oxide resulted in no significant change in the amplitude of the P0-N0 waveform in any of the three montages in which it was recordable (Table 2). While the P0-N0 waveform generally appeared very resistant to the influence of both isoflurane and nitrous oxide, there were individual patients in whom some decay was evident. The reduction was particularly marked in a single patient in whom the P0-N0 amplitude decreased to 79% of baseline during administration of 1.0 MAC/N_2O and to 45% of baseline at 1.5 MAC/N_2O.

Latencies were in general less affected than amplitudes by changing concentrations of isoflurane. However, there was a trend toward a modest increase in latencies with higher inspired concentrations of isoflurane. Significant ($P < 0.05$) differences were observed only for the latency of P0 at the 1.5 MAC/N_2O level in FPz–C2S and for the latency of P1 at 1.5 MAC/N_2O in Cz'–FPz. Note, however, that in some subjects waveforms became unidentifiable at higher isoflurane concentrations (Table 2). In these instances, no value could be entered for latency, with consequent reductions in *n* and in the power of the statistical analysis of latencies.

Elimination of nitrous oxide during administration of 1.5 MAC isoflurane resulted in substantial and significant ($P < 0.04$) recovery of the amplitude of the cortically generated waveforms P1-N1 and P2-N2 (Table 2 and Fig. 2). In some instances, waveforms that had been unidentifiable during administration of 1.5 MAC isoflurane/60% N_2O reappeared on withdrawal of N_2O. For example, in Cz'–FPz the P1-N1 complex was identifiable in six of eight subjects during 1.5 MAC/N_2O administration but was present in all subjects during 1.5 MAC isoflurane/balance O_2 administration. The amplitude of P0-N0 and the latencies of P0, P1, and P2 were unaffected by elimination of N_2O.

Discussion

The anatomic generators of waveforms recorded from scalp–scalp and scalp–cervical montages after posterior tibial nerve stimulation have not been defined with absolute certainty. However, there is substantial evidence that the P1-N1 and P2-N2 waveforms arise within the sensory cortex (20,21). It is also generally agreed that the positive deflection recorded in scalp–upper cervical derivations (e.g., Cz'–C2S) at a poststimulus latency of approximately 28–32 msec (18,22–25) arises subcortically, probably from medical lemniscus or thalamus (24). As recorded in the present study, the mean latency for this response was 34 msec. However, it is probable that P0-N0 is the same response observed by others at the slightly shorter latencies mentioned earlier. The longer latency is explained by several factors. The population in the present study was on average older and taller than other "normative" populations (cf. Kakigi et al. [23]). In addition, the present data were recorded in anesthetized subjects at a slightly subnormal body temperature (35.5°C). Latencies for the P0 response similar to those seen herein have been observed by others in anesthetized subjects (26). Furthermore, the high filter in this study was more restrictive (750 Hz) than that commonly used in electrophysiology laboratories, and this causes an increase in the apparent latency of high-frequency responses (25,27).

Isoflurane was selected for study because it is probably the most widely used volatile agent in settings where intraoperative evoked response recording is performed. In addition, our previous experience with both intravenous and inhaled agents during recording of SSERs to median nerve stimulation indicated that it is isoflurane that has the greatest effect on evoked responses (1,2,6,8). Nonetheless, it must be noted that this study has examined the influence of only isoflurane and nitrous oxide, and it is possible that the considerable resistance of the subcortical response that we have observed may not be apparent in the presence of other agents or combinations of agents.

It has been previously established that spinal somatosensory responses and subcortical responses to other types of stimulation (e.g., the brainstem auditory evoked response) are quite resistant to the influence of anesthetic agents (1,2,15,28–30). However, there has been no prior systematic examination of the effect of anesthetic agents on subcortical SSERs to lower extremity stimulation, nor any simultaneous comparison of cortically and subcortically generated responses. The present study demonstrates that the early subcortical response, P0, is markedly more resistant to the effects of isoflurane and nitrous oxide than are the cortically generated responses that are seen in the more commonly employed scalp–scalp montages, e.g., Cz'–FPz. The latter undergo substantial degradation as end-tidal concentrations of isoflurane administered in conjunction with 60% N_2O increase above 0.5% MAC, whereas the subcortical responses do not. While withdrawal of 60% N_2O during the administration of a constant end-tidal concentration of 1.5 MAC isoflurane resulted in a significant recovery of the amplitude of the responses of cortical origin, there was no effect on the subcortical response. These patterns of anesthetic effect on cortical responses are comparable to those observed by Peterson et al. (6) in a similar protocol that examined the effect of halothane, enflurane, isoflurane, and nitrous oxide on the median nerve SSER.

The present study does not constitute a systematic evaluation of nitrous oxide. It indicates only that the addition of 60% N_2O to 1.0 or 1.5 MAC isoflurane results in a decrease in the amplitude of cortically generated PTSSERs. However, this is in keeping with the observations of the effects of nitrous oxide on cortical evoked responses in other circumstances (12,31). These investigations have consistently revealed amplitude attenuation. In addition, the data permit some insight into the relative effects of equi-MAC concentrations of isoflurane and nitrous oxide. If 60% N$_2$O can be accepted as roughly equivalent to 0.5 MAC, then in this study 1.0 and 1.5 MAC anesthetic levels have been achieved with both isoflurane alone and isoflurane/nitrous oxide combinations. The amplitudes observed during these equi-MAC conditions were very similar. This suggests that equi-MAC concentrations of isoflurane and nitrous oxide have very similar effects on cortical PTSSERs.

The substantial decrease in amplitude (or disappearance) of cortical waveforms observed with increasing concentrations of isoflurane is consistent with other previously published data regarding the effects of volatile anesthetics on evoked responses of cortical origin (3,6,7,29). Collectively, these observations indicate that in the presence of moderate to high concentrations of inhalational anesthetics, cortical PTSSERs will probably be unsatisfactory for spinal cord monitoring. By contrast, the resistance of the P0-N0 subcortical complex to anesthetically induced degradation observed in this study suggests that it may be more useful for intraoperative monitoring. The amplitude of the P0-N0 complex in the Cz′–C2S, Cz′–LM (linked mastoids), and FPz–C2S derivations was sufficient to allow identification even at high levels of isoflurane. Accordingly, this waveform may be especially suitable for monitoring in circumstances where anesthetic depth may fluctuate, particularly as a result of variation in the concentrations of inhaled agents.

Reliance on this subcortically generated response (P0-N0) for intraoperative monitoring is not without limitation. When recorded in adults from surface electrodes as employed in the present study, P0-N0 may be of lesser amplitude than the early complexes of cortical origin (P1-N1, P2-N2). Furthermore, the derivations in which the subcortical response is obtained require electrodes over or near the suboccipital musculature. In our experience, during light anesthesia in the absence of muscle relaxants (e.g., in the time preceding an intraoperative "wake-up" test), these derivations may be contaminated with muscle artifact. Accordingly, at our institution we commonly monitor both the Cz′–FPz and Cz′–C2S or Cz′–LM montages. This allows monitoring of the subcortical response but preserves the option to adjust the anesthetic technique such that the larger P1-N1, P2-N2 complexes can be monitored when the signal-to-noise ratio warrants it.

There are circumstances in which the amplitude of the subcortical response may be larger than was observed in the present study: They may be of larger amplitude in small children (personal communication, W. D. Goldie, MD, Clinical Neurophysiology Laboratory, Children's Hospital of Los Angeles). This is probably because of the relatively shorter distances between the anatomic generator and the recording electrodes. In addition, as mentioned above, we employ a relatively restrictive high filter (750 Hz), and this may attenuate the amplitude of high-frequency responses.

There have been numerous reports of satisfactory intraoperative SSER recording during spinal (4,9,10,33) and aortic (11,13) surgery in which scalp–scalp electrode montages, e.g., Cz′–FPz, have been employed. The use of these montages may be satisfactory when anesthesia-related effects can be controlled and/or are taken into consideration in waveform interpretation. However, when recording and interpretation are being performed without the knowledgeable participation of the anesthesiologist, or in situations where inhaled anesthetics are most appropriate, the use of montages that contain the more robust subcortical components may be advantageous. As is the case with scalp–scalp montages, the montages employed in this study to record the subcortical components used surface electrodes that are simple to apply and that are easily accessible intraoperatively.

Our study also examined the waveforms recordable between leads on the forehead and upper cervical spine. This combination has the minor technical advantage of avoiding the necessity of placing leads within the hairline. While the P0-N0 complex is readily recorded in this lead, cortical waveforms are less easily seen (see Fig. 2). We favor the Cz′–LM or Cz′–C2S configurations because they allow recording of all waveforms (depending on the anesthetic agents in use).

There are alternative techniques for spinal cord monitoring that are not addressed in this study but that may also largely obviate the problem of anesthetic-related degradation of evoked responses. Evoked responses of spinal cord origin can be recorded with needle or other invasive electrodes placed in or adjacent to the surgical field (e.g., epidural space [34], spinous processes [35], and interspinous ligament [15]). The acceptability of these techniques will vary from setting to setting. They represent a somewhat more invasive level of monitoring. Much more important is that these electrodes are in many instances more likely to be dislodged than surface electrodes. Furthermore, electrodes that are readily accessible to the technologist are an advantage in the event of questions regarding recording system fidelity. In addition, some of these techniques may not be applicable during certain exposures, e.g., aortic surgery and anterior approaches to the spinal column. The monitoring of subcortical responses as recorded from scalp–mastoid or scalp–cervical montages using surface electrodes may represent an anesthetic-resistant and widely applicable alternative to these other techniques.

In summary, the present study has examined the effect of three concentrations of isoflurane and 60% nitrous oxide on cortically and subcortically generated evoked responses to posterior tibial nerve stimulation. Both agents cause reductions in the amplitude of the responses of cortical origin of a magnitude that might readily be misinterpreted as representative of neurologic injury. The effect of isoflurane is dose-related. By contrast, the responses of subcortical origin are very resistant to the effect of these two anesthetic agents. For intraoperative spinal cord monitoring, the readily recorded subcortical response may offer advantages over the currently more widely used cortical responses.

We are grateful to the patients who consented to participate in this investigation. We are grateful to John D. Spydell, PhD, of Tracor Northern, who provided the Nomad evoked response apparatus with which this investigation was performed, and to Ted J. Sanford, MD, David O. Peterson, MD, and Celeste Somers, MS, for their contributions to the study protocol. We appreciate the assistance of Sue Moore and Susan Johnson in the preparation of the manuscript.

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Sixty Years Ago In

Anesthesia & Analgesia

B. van Hoosen: Scopolamin (sic) anesthesia in obstetrics. Current Researches in Anesthesia & Analgesia 1928;7:151–4.

The author of this article, Professor and Head of the Department of Obstetrics at Loyala University Medical School, starts with the verity that in the 80 years since Morton introduced either, "there has been a new method for producing anesthesia brought to the attention of the profession on an average of at least once every ten years." True in 1928; no less true in 1988, a point worth bearing in mind when reading of today's latest miracle anesthetic. Back to Dr. van Hoosen: She acknowledges that "ether, like the eldest born of royalty, wears the crown of safety" (imagine getting an elegant phrase like that past a journal editor in 1988!) but then goes on to describe, defend, and promote obstetrical "narcoanesthesia." Popularly known as twilight sleep, narcoanesthesia consisted of the subcutaneous injection of scopolamine alone (three 0.6 mg injections in 90 minutes) or with morphine 10 mg (with the first dose of scopolamine). Not just a sudden idea on Dr. van Hoosen's part, narcoanesthesia was the predominant method for control of pain during labor in Europe and North America throughout the 1920s and well into the 1930s. To Dr. van Hooten, the advantages of twilight sleep included, in addition to relief of pain, shortening of labor, decreased intra- and postpartum blood loss, but also the ability to prolong analgesia "sufficiently to cover any delivery" (including in one of her patients, 57 consecutive hours of twilight sleep). Dr. van Hoosen also mentions disadvantages. One was that "the patient is not open to suggestions and may, therefore, disarrange the sterile goods at the time of delivery or may show more restlessness than the obstetrician desires". Another was that 30 to 45 minutes were "consumed before the patient could be brought under the influence of narcoanesthesia". No mention of babies floppy or blue, or any other problems. That a generation of idiots did not result is testimony to how resilient the human body can be even in the face of a pharmacologic assault such as morphine and scopolamine in doses adequate to assure that the new mother never remembered her labor.

Hepatic Protection from Chemical Injury by Isoflurane

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GIL F, FISEROVA-BERGEROVA V, ALTMAN NH. Hepatic protection from chemical injury by isoflurane. Anesth Analg 1988;67:860–7.

Isoflurane inhibits oxidative metabolism of halothane. Because hepatotoxicity of chemicals may be associated with their metabolism, whether isoflurane can protect the liver against chemical injury was investigated. Hepatic injury was produced in female F344 rats by a 30-minute exposure to 250 ppm of carbon tetrachloride. In this and all other parts of the study, the inspired oxygen concentration was maintained at 21%. The injury was accompanied by elevated activity of liver enzymes in serum (SGOT, SGPT, and SDH), enlarged liver, fatty infiltration of the liver, and vacuolar degeneration of hepatocytes. These signs of toxicity were partly or completely suppressed by concurrent exposure to subanesthetic concentrations of isoflurane (0.2 or 0.038%, respectively). The protective effect was concentration-dependent. Enflurane was protective, but less so than isoflurane. Nitrous oxide and fentanyl had no protective effect.

Key Words: LIVER—hepatotoxicity, carbon tetrachloride. ANESTHETICS, VOLATILE—isoflurane, enflurane. ANESTHETICS, GASES—nitrous oxide. ANALGESICS—fentanyl.

We have demonstrated in rats that oxidative metabolism of halothane is inhibited in the presence of isoflurane (1,2). The inhibition is reversible and dose-dependent. It was speculated that isoflurane can protect the liver from the toxic effect of some drugs and chemicals by inhibiting oxidative metabolism (1,3). However, Fassoulaki et al. (3) found that isoflurane failed to prevent hepatic injury produced by halothane in hypoxic rats pretreated with phenobarbital. This failure can be explained by the complexity of the animal model used for production of liver injury by halothane. In the model used by Fassoulaki et al., hepatic injury was the result of the interaction of three factors: hypoxia, liver enzyme induction, and halothane exposure. Some investigators (4–6) consider hypoxia the most important factor in the development of liver injury by halothane. Thus, the model used by Fassoulaki et al. does not allow study of the effect of halothane by itself.

To resolve the question as to whether isoflurane can or cannot protect the liver from chemical injury, an intrinsic hepatotoxicant was used in the present study. Hepatic injury was induced in female F344 rats by a 30-minute exposure to carbon tetrachloride. Carbon tetrachloride is known to be a potent hepatotoxicant, the toxicity of which is attributed to haloperoxyl radicals formed in the liver by extraction of one chloride ion from the molecule. The process is activated by the mixed-function oxidase system (7). Binding of haloperoxyl radicals to fatty acids initiates lipoperoxidation, which leads to destruction of hepatocyte membranes (8–10). Consequently, intracellular liver enzymes leak out through the damaged cell membranes into serum, hepatic injury being associated with reduced activity of these enzymes in liver and increased activity in serum.

In this study, the measures of the toxic effect of carbon tetrachloride exposure were elevated activity of three liver enzymes in serum (SDH, SGPT, and SGOT), fatty infiltration of the liver, and vacuolar degeneration of hepatocytes. Concurrent exposures to subanesthetic concentrations of isoflurane were used to determine whether isoflurane might protect the liver from injury. Similar exposures to enflurane, nitrous oxide, and fentanyl were used for comparison.

Methods

Experimental Animals

Female F344 rats from Charles River Laboratories, weighing approximately 220 g, were used. Rats were

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This study was supported by Anaquest, a Division of BOC, Inc.
Received from the Departments of Anesthesiology and Pathology, University of Miami School of Medicine, Miami, Florida. Accepted for publication January 22, 1988.

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Table 1. Exposure Protocol Used in 15 Experiments

	TWA concentration during 30-min exposure		
Experiment No./shipment	CCl_4 (ppm)	Coexposure or treatment	Consecutive 2-hr exposure
1/I	474	None	None
2/I	464	0.39% isoflurane	None
3/II	221	None	None
4/II	226	0.185% isoflurane	None
5/II	219	0.23% isoflurane	0.16% isoflurane†
6/II	231	0.038% isoflurane	None
7/II	231	0.038% isoflurane	0.06% isoflurane
8/III	250	None	None
9/III	236	0.19% enflurane	None
10/III	246	50% nitrous oxide	None
11/III	274	0.02 mg fentanyl*	None
12/II	None	None	0.16% isoflurane†
13/III	None	0.19% enflurane	None
14/III	None	50% nitrous oxide	None
15/III	None	0.02 mg fentanyl	None
Controls	None	None	None

Rats used in the experiments were received in three different shipments, as indicated by the Roman numerals. Time-weighted average (TWA) concentrations during a 30-minute exposure to vapors of carbon tetrachloride and/or to an anesthetic and during a 2-hour consecutive exposure to isoflurane are shown. Consecutive exposure immediately followed the 30-minute exposure. Oxygen in all mixtures was maintained at 21%.

*Fentanyl was injected 15 minutes before exposure to carbon tetrachloride (see text).

†Rats in experiments 5 and 12 underwent the 2-hour exposure together.

obtained in three shipments. Rats from the first two shipments were used in the experiments to investigate the effect of isoflurane. Rats from the third shipment were used to investigate the effects of other drugs (Table 1). The rats were maintained in our animal facility for at least 6 weeks on a Purina Lab Chow diet and drinking water ad libitum before the experiments started. Animals were cared for and the experiments performed using standards described in PHS Publication 86-23, Guide for the care and use of laboratory animals. Food was withheld for 12 hours prior to the exposure.

Exposure

Five rats at a time were placed in the exposure chamber, a 20-L glove box through which the gas mixture flow was 2 L/min. The chamber and gas mixture delivery system were the same as in our previous study (1). Fifteen experiments were performed. The liver damage was induced by a 30-minute exposure to approximately 250 ppm of carbon tetrachloride in clean air (compressed air of breathing quality), except for the first two experiments, in which the concentration was doubled. In three experiments, rats were exposed to carbon tetrachloride only; in the other experiments they were exposed to mixtures of carbon tetrachloride and one of the following anesthetics: isoflurane, enflurane, or nitrous oxide. In two experiments the exposure to isoflurane continued for 2 hours after termination of carbon tetrachloride exposure. The oxygen concentration was maintained at 21% in all experiments. The experimental protocol, including the exposure concentrations used in the 15 experiments, is summarized in Table 1. Concentrations of carbon tetrachloride and anesthetic vapors were monitored at 5-minute intervals. Nitrous oxide, along with the appropriate amount of oxygen, was delivered into the chamber from an Ohio-Heidbrink Kinet-O-Meter with no further monitoring. Oxygen concentration was monitored using a Beckman D2 oxygen analyzer. The temperature in the chamber fluctuated between 21 and 25°C. In experiments in which rats were treated with fentanyl, 0.1 ml Innovar-Vet (Pitman-Moore, diluted 1:1) was injected IM in the gluteal region 15 minutes before exposure to carbon tetrachloride. The injection represented 0.02 mg of fentanyl. (Each milliliter of Innovar-Vet contains 0.4 mg of Sublimaze (fentanyl) and 20 mg of droperidol with 1.8 mg of methylparaben and 0.2 mg of propylparaben as preservatives.)

Control Experiments

Fifteen unexposed and untreated rats (controls) and 20 rats treated with one of the agents under consideration for a protective effect (experiments 12–15) were used as control groups. The concentrations and dosages of the agents used in the control experiments were similar to the concentrations and dosages used to evaluate possible protection of liver from injury induced by carbon tetrachloride (Table 1).

Biological Specimens

Twenty-four hours after exposure (or injection of fentanyl), rats were anesthetized with ethyl ether and blood was drawn by cardiac puncture. One aliquot of blood (about 5 ml) was used for measurement of sorbitol dehydrogenase activity (SDH). The other aliquot (about 4 ml) was used for measurement of aminotransferase activities (SGOT and SGPT). The rats were then decapitated, and the liver and kidney were weighed, dissected, and submerged in 10% neutral buffered formalin for histologic examination. At the same time, specimens were also obtained from a control rat that was given neither treatment nor carbon tetrachloride exposure.

Analytical Procedures

Monitoring of Gases in the Exposure Chamber

Fifty microliters of air drawn from the exposure chamber was injected on the gas chromatographic column (1). A Varian 3700 gas chromatograph equipped with flame ionization detector and 1.8-m glass column packed with n-octane on Porasil C (100–120 mesh) was used (column temperature 125°C).

Determination of Sorbitol Dehydrogenase (SDH) Activity

SDH activity was measured in fresh serum using a Sigma Diagnostics kit and Varian Cary 118 UV spectrophotometer. The technique is based on the following reaction:

$$\text{D-Fructose} + \text{NADH} \overset{\text{SDH}}{\leftrightarrows} \text{D-Sorbitol} + \text{NAD}.$$

The decrease in absorbance at 340 nm is a measure of the consumption of NADH by the reaction, and thus of the activity, of SDH. The absorbance measurements were converted into sigma units (SU), by multiplying the change in absorbance per minute by a factor of 58,000 (11). Sera from rats with high SDH activity were properly diluted, and the appropriate dilution factor was incorporated in the calculation. The measurements were made at 25°C. The analyses were done within 3 hours after blood was withdrawn.

Determination of Serum Aminotransferase Activity

SGOT and SGPT activities in serum were measured within 5 hours after blood was withdrawn. SGOT measurements are based on reversible transamination from aspartate to α-ketoglutarate, which produces oxaloacetate and glutamate. SGPT measurements are based on reversible transamination from the L-alanine to the α-ketoglutarate, which produces pyruvate and L-glutamate. The activities of the two enzymes were determined by measuring the disappearance of NADH at 340 nm (12). Enzyme activity is expressed in international units (IU).

Histological Examination

The liver and kidney from each rat were dissected and processed on a Fisher Histomatic Tissue Protector. Tissues were then embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin using standard procedures.

Statistical Analysis

Means, standard deviations, and standard errors were calculated and nonpaired two-tailed *t*-tests were made on an IBM-XT computer using the Epistat program. When the variances of the compared samples largely differed, the Wilcoxon rank sum test (independent, two-tailed) was used.

Results

Exposure Levels and Health Status of Rats

The time-weighted average concentrations (TWA) in the exposure chamber are shown in Table 1. TWAs were calculated from six measurements taken during each 30-minute exposure and 10 measurements taken during each 2-hour exposure. The individual measurements deviated from TWA $<$ 10% with the exception of the measurements in samples taken within the first 5 minutes of exposure. In these samples the concentrations were about 50% of TWA. Oxygen concentrations fluctuated between 20 and 21%.

The rats appeared normal except for those given fentanyl or exposed to high concentrations of carbon tetrachloride. Rats given fentanyl were anesthetized and rigid for 5–12 hours after the injection. Rats exposed to 470 ppm of carbon tetrachloride were in light (experiment 1) or deep (experiment 2) levels of anesthesia during the exposure and recovered within 5 minutes after termination of the exposure. Autopsy revealed that one rat in experiment 1 had a lung tumor. This rat was excluded from the study.

Control Experiments

In rats treated only with anesthetic agents, but not with carbon tetrachloride, all measures of liver damage (i.e., activity of liver enzymes in serum [SDH, SGOT, and SGPT]) and liver weight remained in the range of values of the unexposed controls (Table 2). Gross examination and histologic examination of liver and kidneys revealed no abnormalities, with the exception of an occasional appearance of chronic active inflammation in the liver, which was observed to the same extent in all groups as in controls.

Table 2. Results of Laboratory Analyses

Experiment no.	Treatment during exposure to CCl_4	Body weight (g)	Percent of body weight		SDH (SU)	Activity (IU)	
			Liver	Kidney		SGOT	SGPT
	Rats exposed to 470 ppm carbon tetrachloride*						
1	None (n = 4)	186 ± 17	3.27 ± 0.28†	0.71 ± 0.03†	33811 ± 11504†	3444 ± 1397†	4221 ± 1808†
2	0.39% isoflurane	199 ± 10	3.22 ± 0.10†	0.66 ± 0.03	6721 ± 1515†	705 ± 222†	1059 ± 245†
	Rats exposed to 250 ppm carbon tetrachloride*						
3	None	221 ± 14	3.12 ± 0.05†	0.65 ± 0.03	3970 ± 1694†	295 ± 92†	375 ± 139†
4	0.185% isoflurane	210 ± 14	2.64 ± 0.18	0.66 ± 0.02	248 ± 69†	175 ± 53	82 ± 15
5	0.23% isoflurane‡	219 ± 4	2.93 ± 0.25	0.63 ± 0.03	240 ± 116†	158 ± 39	75 ± 5
6	0.038% isoflurane	213 ± 11	3.19 ± 0.30†	0.66 ± 0.02	1129 ± 274†	201 ± 29†	195 ± 49†
7	0.038% isoflurane‡	209 ± 3	2.96 ± 0.10	0.62 ± 0.03	1619 ± 2359†	315 ± 299†	380 ± 436†
8	None	217 ± 9	3.27 ± 0.22†	0.64 ± 0.06	5147 ± 4024†	476 ± 256†	679 ± 597†
9	0.19% enflurane	216 ± 10	3.21 ± 0.14	0.62 ± 0.01	1208 ± 196†	167 ± 25	186 ± 13†
10	50% nitrous oxide	221 ± 12	2.94 ± 0.10	0.62 ± 0.02	3060 ± 1284†	319 ± 168†	548 ± 351†
11	0.02 mg fentanyl	213 ± 11	3.04 ± 0.26	0.63 ± 0.03	7172 ± 4192†	882 ± 625†	1316 ± 1072†
	Rats not exposed to carbon tetrachloride						
12	0.16% isoflurane§	211 ± 4	2.74 ± 0.11	0.64 ± 0.02	107 ± 24	156 ± 71	65 ± 13
13	0.19% enflurane	211 ± 9	2.71 ± 0.09	0.63 ± 0.03	144 ± 45	184 ± 75	81 ± 17
14	50% nitrous oxide	214 ± 13	2.83 ± 0.28	0.60 ± 0.02	159 ± 68	138 ± 40	80 ± 15
15	0.02 mg fentanyl	215 ± 10	2.55 ± 0.12	0.61 ± 0.04	105 ± 41	174 ± 48	72 ± 11
Controls	None (n = 15)	216 ± 13	2.81 ± 0.21	0.63 ± 0.03	139 ± 45	144 ± 54	74 ± 15

Mean ± SD; unless otherwise noted, n = 5.

Abbreviations: SU = sigma units; IU = international units.

*For the exact carbon tetrachloride concentration used in each experiment, see Table 1.

†The value is significantly larger compared to controls ($P < 0.01$). The significance in differences between the experiments is given in text.

‡Consecutive 2-hour treatment with isoflurane.

§Two-hour exposure.

Liver Damage Induced by Exposure to Carbon Tetrachloride Only

In experiments 1, 3, and 8, liver damage was evidenced by enlarged livers, elevated activity of liver enzymes in serum (Table 2), and histopathologic findings (Table 3). All differences in liver weight and activity of all three enzymes between exposed rats and controls were statistically significant ($P < 0.01$). Massive fatty infiltration was found in all livers on gross examination. Histologic examination of liver revealed vacuolar degeneration of hepatocytes, mainly around the central veins. The vacuolated hepatocytes were usually surrounded by an infiltrate composed of histiocytes, lymphocytes, and occasional neutrophils. Cytoplasmic vacuolar degeneration of hepatocytes caused the cells to swell and compress adjacent hepatocytes. Some of the degenerating hepatocytes progressed to necrosis. In areas with necrotic hepatocytes, neutrophils predominated in the infiltrate.

The concentrations of carbon tetrachloride to which rats in experiments 3 and 8 were exposed were almost the same (Table 1). Because the difference in enzyme activity and liver weight between these groups was not statistically significant ($P > 0.1$), data from experiments 3 and 8 were combined and used as "untreated group" in statistical analysis (Fig. 1).

Activities of the three enzymes measured were more elevated in the serum of rats exposed to 474 ppm of carbon tetrachloride (experiment 1) than in rats exposed to about 250 ppm (experiments 3 and 8). The difference was statistically significant ($P < 0.01$). Histologic examination of liver revealed more extensive necrosis at the higher exposure. Thus it appears that the intensity of liver damage is dose-dependent. Kidney enlargement, measured as a fraction of body weight, was observed in all four rats used in experiment 1. The increase was statistically significant compared to controls ($P < 0.01$) and rats treated with isoflurane ($P < 0.05$). On histologic examination no abnormalities were noted.

Liver Protection by Isoflurane

In experiments 2 and 4–7, liver damage was induced by exposure to two concentrations of carbon tetrachloride:

1. During the exposure to about 470 ppm of carbon tetrachloride, isoflurane significantly ($P < 0.02$) reduced the elevation of activity of all three liver enzymes in serum (Table 2). Histologic examination revealed degenerative changes in both groups; however, necrosis in the liver of rats

Table 3. Results of Histologic and Gross Examination of Liver

Experiment no.	Treatment during exposure to carbon tetrachloride	Histologic examination			Gross examination (Fatty infiltration)
		Necrotic cells	Vacuolar degeneration	Chronic active inflammation	
	Rats exposed to 470 ppm carbon tetrachloride*				
1	None ($n = 4$)	++	+	+	++
2	0.39% isoflurane	+	+	+	++
	Rats exposed to 250 ppm carbon tetrachloride*				
3	None	+	++	++	++
4	0.185% isoflurane			+	
5	0.23% isoflurane†			+	−+
6	0.038% isoflurane	++	++	++	+
7	0.038% isoflurane†	++	++	++	
8	None	+	+	++	++
9	0.19% enflurane	+	+	+	−+
10	50% nitrous oxide	+	++	++	++
11	0.02 mg fentanyl	++	++	++	+
	Rats not exposed to carbon tetrachloride				
12	0.16% isoflurane‡			+	
13	0.19% enflurane			+	
14	50% nitrous oxide			+	
15	0.02 mg fentanyl			+	
Controls	None ($n = 15$)			+	

Scale of observed pathologic changes: + = mild; ++ = moderate; +++ = extensive; ++++ = severe. Average grading of each group is indicated. Unless otherwise noted, $n = 5$.

*For the exact carbon tetrachloride concentration used in each experiment, see Table 1.

†Consecutive 2-hour treatment with isoflurane.

‡Two-hour exposure.

protected by isoflurane was less severe (Table 3). Kidney enlargement did not occur in rats treated with isoflurane. These observations prove that isoflurane partially protects liver from injury induced by anesthetic concentrations of carbon tetrachloride.

2. During exposures to about 250 ppm of carbon tetrachloride, isoflurane was administered at two concentrations: at a concentration 10 times higher than carbon tetrachloride, and at a concentration similar to the concentration of carbon tetrachloride. Administered at a high concentration, isoflurane completely suppressed the toxic effects of carbon tetrachloride (experiments 4 and 5). Livers of treated rats were not enlarged (Table 2), and the activity of liver transaminases in serum was not significantly elevated (Fig. 1). The statistically significant elevation of SDH is too small to be of biological significance. Gross and histologic examinations of liver revealed no pathological changes (Table 3).

Administered at a concentration similar to the concentration of carbon tetrachloride, isoflurane does not fully protect the liver (experiments 6 and 7). The activity of the three liver enzymes in serum was significantly elevated. The elevation of SDH activity was significantly less in treated rats than in untreated rats ($P < 0.01$), but the activities of SGOT and SGPT were unaffected by the treatment ($P > 0.05$) (Fig. 1). Histologic examination revealed no reduction of liver damage. On gross examination, no fatty infiltration was apparent. Livers were enlarged in experiment 6 but not in experiment 7 (Table 2). Extended exposure to isoflurane did not otherwise contribute to the protection.

Liver Protection by Other Agents

In experiments 9 to 11, liver damage was induced by exposure to about 250 ppm of carbon tetrachloride. Data are shown in Tables 2 and 3 and in Figure 1.

Treatment with 0.19% enflurane significantly reduced the elevation of SDH activity and suppressed the elevation of SGOT activity (Fig. 1). Reductions of SDH and SGOT activity were statistically significant compared to the untreated group ($P < 0.05$). SGPT activity was unaffected by the treatment ($P > 0.5$). Histologic examination of liver revealed that lesions were of the same type as those seen in untreated rats, but the intensity of the reaction was less severe. Fatty infiltration was mild, and no liver enlargement was demonstrated ($P > 0.7$).

Treatment with 50% nitrous oxide had no affect on the activity of the three liver enzymes in serum. The

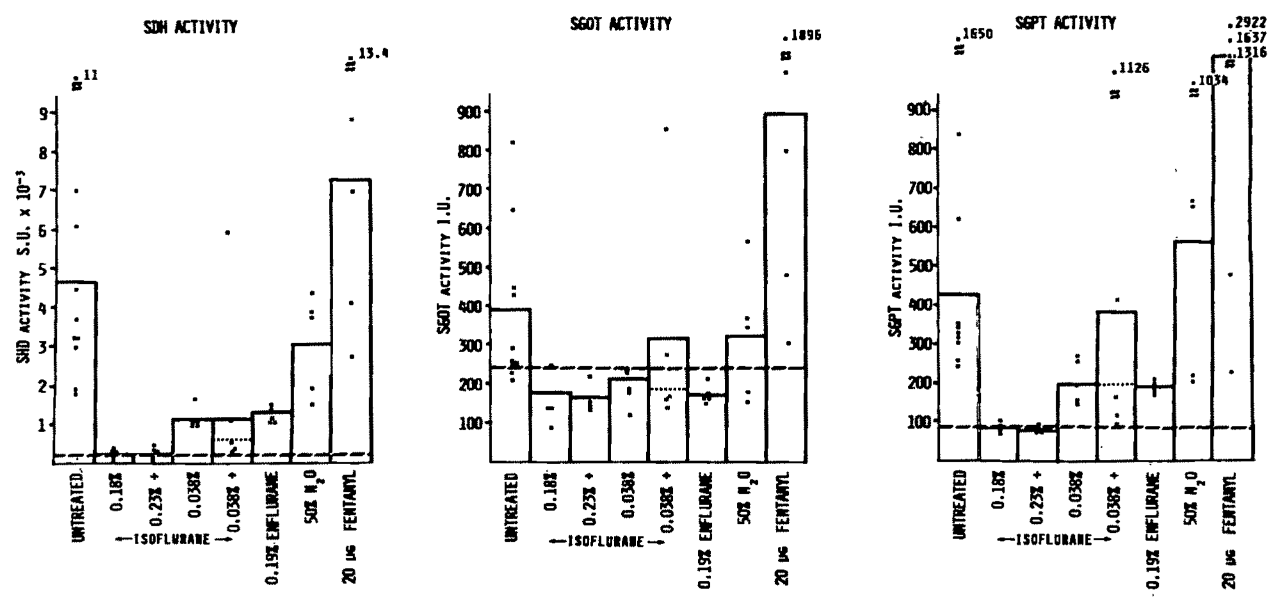

Figure 1. Activity of liver enzymes in serum of rats obtained 24 hours after a 30-minute exposure to approximately 250 ppm of carbon tetrachloride alone or in the presence of one of the studied anesthetics. The concentrations of anesthetics are indicated below the bars. "+" after the concentration indicates that the exposure to isoflurane continued for 2 hours after the end of the exposure to carbon tetrachloride. The dots represent the individual measurements, and bars indicate their means. Dotted lines represent means with one extreme high value excluded. Dashed lines indicate upper limits of background levels. SDH is serum sorbitol dehydrogenase expressed in sigma units. SGOT is serum glutamic-oxalacetic transaminase, and SGPT is serum glutamic-pyruvic transaminase, both expressed in international units.

activities were significantly elevated compared to controls ($P < 0.01$) and were not significantly different compared to the untreated group ($P > 0.1$). Histologic examination revealed changes similar to the changes in the untreated group. Intensity of fatty infiltration was comparable to that of the untreated group. Liver enlargement was not present.

Fentanyl treatment had no significant effect on the activities of SDH and SGPT ($P > 0.1$ as compared with the untreated group). However, a significant enhancement of SGOT activity was demonstrated ($P < 0.05$). Histologic examination revealed more severe necrosis than in the untreated group. Fatty infiltration was apparent. No liver enlargement was demonstrated.

Discussion

This study demonstrates that isoflurane can protect the liver from chemical injury induced by an intrinsic hepatotoxicant such as carbon tetrachloride. To provide such protection, isoflurane must be administered at the same time as carbon tetrachloride, and for effective protection it must be administered at a higher concentration than carbon tetrachloride. Of the other three anesthetics used in this study, only enflurane (which has a chemical structure similar to that of isoflurane) protected the liver from chemical injury. Based on the two studies in which either isoflurane or enflurane was administered at about one-tenth of MAC, the protection by enflurane was less complete than the protection afforded by isoflurane. Nitrous oxide and fentanyl had no protective effect, which indicates that the protection is not associated with the anesthetic effect.

Isoflurane is an anesthetic devoid of hepatotoxicity (13). In comparison to other volatile anesthetic agents, isoflurane is considered an inert drug that undergoes very little metabolism either in vitro (14) or in vivo in humans (15) or in animals (16). The involvement of cytochrome P-450 and the mixed-function oxidase system in the little metabolism of isoflurane that does occur has been documented (14). It has been suggested that isoflurane uncouples the cytochrome P-450 and the mixed-function oxidase system and either dismutates hydrogen peroxide or inhibits its formation (14). The two suggested involvements of isoflurane can be used to explain its protective effect against chemical injuries observed in this study.

1. When the cytochrome P-450 enzyme system is disarranged by isoflurane, the metabolism of carbon tetrachloride is suppressed and consequently the liver damage is diminished.
2. If isoflurane dismutates haloperoxyl radicals, as suggested for hydrogen peroxide, the destructive consequences of lipoperoxidation can be prevented.

Table 4. Liver Injury in Male F344 Rats Caused by a 30-Minute Exposure to 232 ppm Carbon Tetrachloride or to a Mixture of 235 ppm Carbon Tetrachloride and 0.19% Isoflurane

		Liver enzyme activity in serum				
Exposure	Liver weight (% of body wt)	SDH (SU)	SGOT (IU)	SGPT (IU)	Fatty infiltration	Vacuolar degeneration*
CCl_4	4.19 ± 0.97	457 ± 250	112 ± 38	83 ± 48	++	++
Mixture	3.56 ± 0.58	278 ± 303	169 ± 63	93 ± 51	+	
None	3.28 ± 0.24	234 ± 112	183 ± 73	122 ± 51		

Mean ± SD; $n = 4$.

All measurements and observations were made in specimens collected 24 hours after the end of exposure. Scale of observed pathological changes is the same as in Table 3. The differences among the groups are statistically insignificant ($P > 0.05$).

*No necrotic hepatocytes were found.

However, these explanations of the protective mechanism are speculative and beyond the scope of this study.

Our previous studies demonstrated that, in the presence of isoflurane, oxidative metabolism of halothane is greatly inhibited and reductive metabolism is unaffected (1,2). We speculated that the altered metabolism might affect the toxicity of halothane and possibly of other hepatotoxicants. The hepatotoxic effect of halothane is associated with a special vulnerability of the affected individual rather than with the intrinsic toxicity of halothane (17). To study toxicity of such a hepatotoxicant is a cumbersome task, because the toxic effect rarely appears and is unpredictable. To overcome this uncertainty, a rather artificial animal model has been developed for studies of halothane hepatotoxicity (4). In this model, halothane metabolism is enhanced by induction of the mixed-function oxidase activity by phenobarbital pretreatment, and hypoxia is used to promote lipoperoxidation (10,17,18). As a result of these drastic treatments, conditions favorable to the development of liver injury are created. These conditions, however useful for the study of toxicity mechanisms, may not be suitable for toxicological studies. The failure of isoflurane to protect the liver from halothane injury in the study by Fassoulaki et al. (3) can be attributed to the unphysiologic conditions of the animal model. It remains to be seen whether or not isoflurane can protect against halothane injury to the liver of albino Amana and Hartley guinea pigs, which were recently shown to be vulnerable to halothane-induced hepatic damage under normal conditions (19).

To answer the question as to whether isoflurane can protect the liver against chemical injury, we searched for an intrinsic (predictable) hepatotoxicant that, when administered by inhalation, can produce a measurable acute liver injury at a concentration with minimal or no anesthetic effect. Female F344 rats exposed to carbon tetrachloride met these criteria. Measurable liver injuries are produced by a 30-minute exposure to 250 ppm of carbon tetrachloride. Such exposure did not affect the motor activity or behavior of the rats. Liver injury was manifested by symptoms typical of carbon tetrachloride intoxication (20). Liver injury became more severe when the exposure concentration was doubled. However, at the higher concentration, the motor activity of the rats was significantly inhibited, and we were concerned that uptake and distribution of the inhaled chemicals could be altered due to suppressed respiratory and cardiovascular functions. For this reason an exposure to 250 ppm was preferred in this study. It is possible, however, that due to long-lasting anesthesia the ventilation of rats treated with Innovar was inadequate and hypoxia increased the liver's vulnerability to chemical injury. Thus, in spite of the fact that Innovar administration produced no liver injury, hypoxia could potentiate toxicity of carbon tetrachloride, as demonstrated by the increased SGOT activity and severe liver necrosis in rats treated with Innovar shortly before carbon tetrachloride exposure.

Female rats were preferred in this study for two reasons: 1) The liver enzyme activity in serum and the histologic examination of liver revealed that the liver injuries were more severe in female rats than in male rats (compare Table 4 with Tables 2 and 3). 2) Because SDH is present in a large quantity in liver and not in other tissues, SDH activity is the most specific indicator of liver injury (20–22). It is also a sensitive indicator of hepatic injury by carbon tetrachloride (23). However, small quantities of SDH are also present in the kidneys and testicles (17). To eliminate the possibility of interference of SDH originating from the testicles, female rats were used in this study. The enzyme activity was measured 24 hours after exposure, as it seems that the elevation peaks at that time (20,21). In our pilot study, Swiss female mice were similarly exposed to carbon tetrachloride and to mixtures of carbon tetrachloride and isoflurane. The exposures affected the SDH activity in serum to the same extent as described here for female rats. Mice were not used in this study because we were unable to obtain a sufficient amount of blood for the determination of all three liver enzymes.

Interaction of carbon tetrachloride with numerous hepatotoxic chemicals has been described (24). The changes in toxicity were usually associated with an altered activity or availability of mixed-function oxidase prompted by competitive inhibition, mixed-function oxidase induction, or destruction of cytochrome P-450. The protective mechanism of isoflurane and enflurane observed in this study is not likely to be explained by any of these mechanisms. The interaction of isoflurane and enflurane with carbon tetrachloride, however, resembles the interaction of carbon tetrachloride with 1,3-dichloro-2-propanone, which is also nonhepatotoxic, does not destroy cytochrome P-450, yet protects liver against injury by carbon tetrachloride (25). The mechanism by which 1,3-dichloro-2-propanone protects liver from carbon tetrachloride injury is unknown.

The technical assistance of Mary Ann Gil is gratefully acknowledged.

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Barbiturate Anesthesia and Alcohol Tolerance in A Rat Model

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CURRAN MJA, NEWMAN LM, BECKER GL. Barbiturate anesthesia and alcohol tolerance in a rat model. Anesth Analg 1988;67:868–71.

Anesthetic responses to a variety of barbiturates were examined in adult male rats rendered alcohol-tolerant by administration of an ethanol-containing balanced liquid diet for 3 weeks. Within 9 hours of withdrawing the diets, groups of 10–15 ethanol-fed rats and pair-fed controls were injected intraperitoneally with one of the following drug/dose combinations: thiamylal 20, 40, or 60 mg/kg; methohexital 10, 20, or 40 mg/kg; secobarbital 20, 30, or 40 mg/kg; pentobarbital 10, 20, or 40 mg/kg; or phenobarbital 80, 120, or 160 mg/kg. Each animal was monitored for time to loss of righting reflex (onset of anesthesia), absence of response to a painful stimulus (analgesia), and sleeping time (duration of anesthesia). None of these three anesthetic responses differed significantly in ethanol-fed and control rats with any dose of thiamylal, methohexital, or secobarbital. In contrast, all three responses were significantly less in rats given the middle dose of pentobarbital (20 mg/kg) than they were in control rats. Onset and duration of anesthesia were also shorter with the middle dose of phenobarbital (120 mg/kg), but analgesia was not. The results of this study, in combination with others, suggest that 1) cross-tolerance to anesthetic effects of barbiturates in ethanol-tolerant rats is not uniform with all barbiturates: and 2) because shorter-acting barbiturates show negligible cross-tolerance with alcohol, higher doses of these agents may not be required for satisfactory anesthesia in chronically alcoholic humans.

Key Words: ALCOHOL—tolerance. HYPNOTICS, barbiturates—interactions with alcohol. INTERACTIONS (DRUG)—barbiturates and alcohol.

Chronic ethanol intoxication produces tolerance to alcohol, including an increase in the ethanol dose required to sustain a constant level of behavioral response. Animals and humans tolerant to ethanol have also been reported to show cross-tolerance to anesthetic effects of other drugs, notably barbiturates. Pentobarbital sleep time has been found to be shortened in ethanol-tolerant rats (1,2) and rabbits (3). Other barbiturates also showed cross-tolerance with alcohol in various measures of anesthetic response (4–6).

Other studies, on the other hand, have failed to detect cross-tolerance to barbiturates in the presence of alcohol tolerance. In contrast to the results cited above, it has also been reported that anesthetic effects of pentobarbital were not significantly attenuated by long-term ethanol treatment in rats (6,7). Induction and maintenance of anesthesia with thiopental (8,9) or methohexital (8) were not affected in alcohol-tolerant rats compared to controls.

The above conflicting results have generally been attributed to differences in treatment and/or testing procedures that might influence outcome (10). One such difference has been the barbiturate used for acute testing of anesthetic responses. For example, the weight of evidence with pentobarbital favors the existence of cross-tolerance with ethanol, whereas both studies with thiopental gave opposite results. The present study was undertaken to examine more systematically the possibility that cross-tolerance with ethanol for selected measures of barbiturate anesthesia is agent- or type-specific within the barbiturate class.

Materials and Methods

Procedures for treatment and testing of animals were identical to those used in a previous study from our laboratory (9). Male Sprague Dawley rats, housed two per cage, were allowed ad libitum access to a

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Received from the Department of Anesthesiology, Michael Reese Hospital and Medical Center, Chicago, Illinois, the Pritzker School of Medicine, University of Chicago, Chicago, Illinois, the Department of Anesthesia, Rush Presbyterian-St. Luke's Medical Center, Chicago, Illinois, and the Department of Anesthesiology, University of Nebraska Medical Center, Omaha, Nebraska. Accepted for publication April 27, 1988.

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complete balanced liquid diet containing 6.54% ethanol (w/w) as their only source of food and water for 3 weeks. The diet consisted of chocolate Sustacal 315 cc, water 151 cc, and 34 cc of 95% ethanol. This level of ethanol, in a complete diet given for 21 days, has been shown to produce tolerance and at the same time permit normal growth and avoid nutritional deficiencies (11,12). Pair-fed controls were given exactly the same volume of diet consumed by their treated counterparts over the previous 24 hours but with sucrose or white dextrin isocalorically substituted for ethanol. All liquid diets were withdrawn at midnight of the 22nd day, 9 hours before testing, and the rats were given free access to water.

Nine hours after withdrawal of rats from their diets, acute testing of anesthetic responses was begun using the following drugs and doses: thiamylal 20, 40, and 60 mg/kg; methohexital 10, 20, and 40 mg/kg; secobarbital 20, 30, and 40 mg/kg; pentobarbital 10, 20, and 40 mg/kg; and phenobarbital 80, 120, and 160 mg/kg. All drugs were administered intraperitoneally. Ten to 15 rats in both the experimental and control groups were tested at each dose level of each drug.

After each rat was injected with anesthetic, it was returned to its cage and observed for loss of righting reflex (induction of anesthesia), defined as failure of the rat, when placed on its back, to roll to a lateral or upright position within 30 seconds. Immediately on loss of righting reflex, sleep monitoring was carried out by placing the rat at the center of an 18-by-24–inch rectangle outlined on the floor and noting the time required for the rat to move out of that area. When the rat did so, it was returned to its cage, and its sleeping time (duration of anesthesia) was recorded as the interval between loss of righting reflex and movement out of the rectangle. At 10 minutes after loss of righting reflex or 20 minutes after injection, if loss of righting reflex had not occurred by that time, analgesia was measured by placing the rat on a heated surface (60°C) and timing the appearance of avoidance behavior (escape from surface or licking of paws). The rat was removed from the surface as soon as avoidance occurred or at 15 seconds, if there was no response by them. Rats which had still been sleeping at the time of analgesia testing were immediately returned to their rectangles for continued sleep monitoring. Rats which had not lost their righting reflex by the time of analgesia testing, and which therefore had not slept, were assigned a sleeping time of zero minutes.

For each measure of anesthesia, response times were considered in relation to a specific reference value. Thus, responses are reported as follows: for loss of righting reflex, the percentage of rats in the group that retained the reflex (remained upright) for at least 10 minutes after injection: for analgesia, the percentage that demonstrated escape/avoidance within 15 seconds; and for sleeping, the percentage that had sleeping times of <10 minutes—i.e., that either stayed awake throughout the observation period or that reawakened within 10 minutes after loss of righting reflex. The results for corresponding treated and control groups were compared using Fisher's exact probability test, with $P < 0.05$ considered statistically significant.

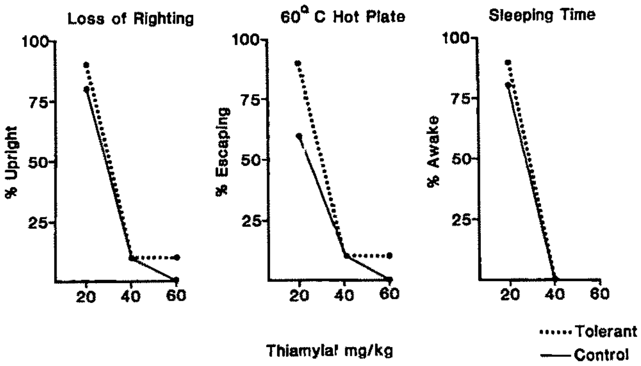

Figure 1. Anesthetic responses of chronically ethanol-fed rats to acutely administered thiamylal. Values on the ordinate are the percentage of animals tested that gave the indicated response. For details of testing procedures, see text.

Results

Over the 3-week feeding period, both alcohol-fed and control rats showed steady weight gains that were not significantly different at the time of the drug testing (data not shown). Our previous study (9) showed that average blood alcohol levels were consistently elevated in the group ingesting alcohol. After withdrawal of alcohol at midnight on the 22nd day, alcohol levels all reached zero within 4½ hours, well before acute drug testing was begun.

We had previously demonstrated that the alcohol-fed rats were alcohol-tolerant at 3 weeks (9). Alcohol-fed rats showed significant attenuation in loss of righting at an alcohol dose of 4.0 g/kg, in pain tolerance at 2.4 g/kg, and in sleeping time at 4.0 g/kg.

Figures 1–3 demonstrate that, when injected with thiamylal, methohexital or secobarbital, there were no significant differences between ethanol-treated rats and controls in any of the three measures of anesthesia. With all three doses of pentobarbital, on the other hand (Fig. 4), all three responses were significantly attenuated in ethanol-treated rats com-

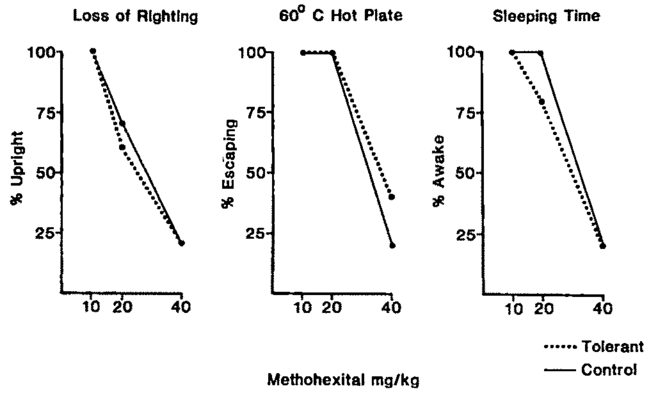

Figure 2. Anesthetic responses of chronically ethanol-fed rats to acutely administered methohexital. See legend to Figure 1.

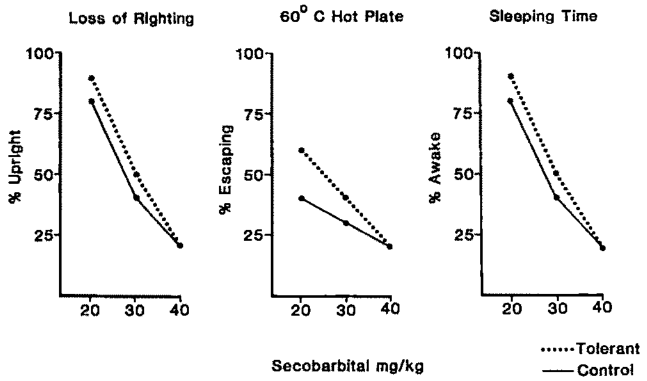

Figure 3. Anesthetic responses of chronically ethanol-fed rats to acutely administered secobarbital. See legend to Figure 1.

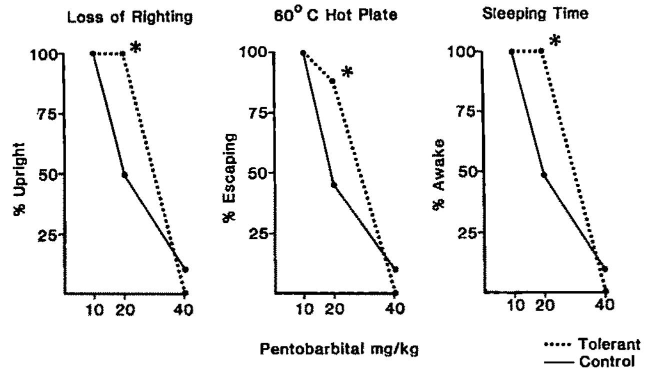

Figure 4. Anesthetic responses of chronically ethanol-fed rats to acutely administered pentobarbital. See legend to Figure 1.

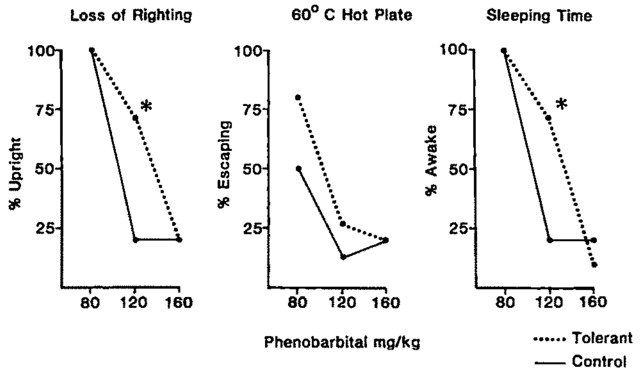

Figure 5. Anesthetic responses of chronically ethanol-fed rats to acutely administered phenobarbital. See legend to Figure 1.

pared to controls. With phenobarbital (Fig. 5) onset and duration of anesthesia were also significantly reduced in the alcohol-fed rats, but analgesia was not significantly affected.

Discussion

The consistent lack of cross-tolerance with ethanol seen in the present study of rats with regard to the anesthetic effects of acutely administered thiamylal, methohexital, and secobarbital is identical to the result we obtained previously with thiopental using this same experimental paradigm (9). This finding is consistent with other studies on short-acting barbiturates, indicating that the latter do not show significant cross-tolerance with alcohol in the production of anesthesia-related responses. In contrast, anesthetic effects of pentobarbital and phenobarbital were significantly attenuated in ethanol-fed rats compared to controls; this result also agrees with most of the published studies on those agents in suggesting that cross tolerance to longer-acting barbiturates does develop with chronic alcohol ingestion.

The existence of a qualitative difference between shorter- and longer-acting barbiturates with respect to behavioral manifestation of alcohol cross-tolerance has been slow to gain acceptance (10). A particular contribution of the present work is that a range of barbiturate types were all studied within the same testing sessions. The differences found between shorter- and longer-acting agents cannot, therefore, be ascribed to methodological variations among different studies or laboratories.

The objective of our study was simply to ascertain the presence or absence of cross-tolerance to alcohol in selected anesthetic responses produced by a range of barbiturate types. Additional studies of a different kind would be necessary to establish the pharmacologic mechanism(s) responsible for the patterns of tolerance documented in this study. Because tolerance represents a loss of proportionality between observed response and administered dose, either reduced sensitivity of target tissue (functional tolerance), or decreased effective concentration of drug (dispositional tolerance), or both, could underlie the changes observed.

Dispositional tolerance, which could be assessed through measurement of blood or tissue levels of barbiturates in parallel with demonstration of tolerance, deserves consideration as an explanation for the cross-tolerance observed in this study. Increased biotransformation of acutely administered barbiturates is known to result after the prior chronic administration of barbiturates and other drugs, including alcohol (13). Such enhanced metabolism could theoretically lower the circulating concentrations of barbiturate and thereby promote dispositional tolerance. Such a mechanism would account for the absence of cross-tolerance with the shorter-acting agents, because their action is governed almost entirely by rapid distribution into and out of the central nervous system (14,15) before equilibration between blood and tissue levels of drug necessary for biotransformation to play a demonstrable role. In contrast, hepatic metabolism is more important in the pharmacokinetics of the longer-acting barbiturates (14), so that liver enzyme induction would indeed be expected to contribute to cross-tolerance observed with latter agents.

Data bearing on the question of altered barbiturate biotransformation in ethanol tolerance have recently been published (6). In rats demonstrated to be ethanol tolerant, blood levels of acutely administered pentobarbital and barbital were not significantly different from controls. Other studies (6) found no statistically significant differences between the control groups and the ethanol-treated groups on the duration of sleep and hypothermic response to pentobarbital. Chronic ethanol treatment produced a marginally significant decrease in pentobarbital-induced ataxia ($P < 0.04$). However, ethanol treatment significantly decreased motor impairment, hypothermic response, and hypnosis in the barbital group. This indicates cross-tolerance between ethanol and barbital, which is essentially non-metabolized. The findings of Gougos et al. (6) suggest that cross-tolerance between longer-acting barbiturates and alcohol may not correlate with the extent to which metabolism is involved in disposition, contradicting our inference that the cross-tolerance differences observed between shorter- and longer-acting barbiturates in our present study are likely to reside in the greater influence of hepatic metabolism in the disposition of longer acting barbiturates. Although no shorter-acting barbiturates were examined by Gougos et al. (6), they found, as we did, clear-cut differences among barbiturates within the same study, in support of the conclusion that cross-tolerance to anesthesia-related effects of barbiturates in the presence of ethanol-tolerance is not a uniform characteristic of barbiturates.

In summary, the results of this animal study, in combination with others previously published, suggest that shorter-acting barbiturates show negligible cross-tolerance with alcohol in their effects on representative measures of anesthesia. Subject to confirmation in controlled clinical studies, we predict no need for increased doses of the shorter-acting barbiturates currently in clinical use to achieve satisfactory anesthesia in chronic alcoholic patients who are not acutely intoxicated. In contrast, in the present study two longer-acting barbiturates did show diminished anesthetic responses in ethanol-fed rats; elucidation of the relative contributions of functional and dispositional components to the cross-tolerance shown by these agents will require additional studies.

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The Pharmacokinetics of Bupivacaine When Injected Intra-articularly After Knee Arthroscopy

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KATZ JA, KAEDING CS, HILL JR, HENTHORN TK. The pharmacokinetics of bupivacaine when injected intra-articularly after knee arthroscopy. Anesth Analg 1988;67:872–5.

Bupivacaine pharmacokinetics were determined in 11 patients receiving the drug intra-articularly after knee arthroscopy performed under general anesthesia. Forty ml 0.25% bupivacaine was given at the end of surgery and the thigh tourniquet was released 2 to 3 minutes after injection. Blood samples were obtained up to 5 hours after tourniquet release and plasma bupivacaine concentrations were determined. Pharmacokinetic parameters determined were (mean ± SD): volume of distribution (V_d beta) 206 ± 88 L, clearance (Cl) 0.816 ± 0.378 L/min, terminal half-life ($T_{1/2}$) beta 189 ± 84 minutes, absorption rate constant (k_a) 9.92 ± 6.79/min, estimated peak plasma concentrations (Cp_{max}) 0.48 ± 0.20 μg/mL, and time to peak concentration (t_{max}) 43.4 ± 23.1 minutes. Results indicate that injections of 100 mg bupivacaine intra-articularly after knee arthroscopy produce peak blood concentrations within the first hour after surgery, and that these will be well below concentrations associated with toxic reactions. Peak concentrations can be minimized with shorter tourniquet inflation times and with longer intervals between injection and tourniquet release.

Key Words: PHARMACOKINETICS—intra-articular bupivacaine. SURGERY—arthroscopy.

Bupivacaine, a long-acting, highly lipid soluble local anesthetic, is frequently injected intraoperatively to provide postoperative analgesia (1). Intra-articular bupivacaine has been used not only to provide local anesthesia during knee arthroscopy (2,3), but many orthopedic surgeons also inject bupivacaine intra-articularly at the end of arthroscopic procedures performed under general anesthesia. Because the duration of bupivacaine action is 2 to 4 hours (1), it is believed that a period of postoperative analgesia can be achieved with such injections. Though plasma bupivacaine concentrations after its administration into the knee joint have been reported (2,3), the data do not permit formal pharmacokinetic analysis. We therefore sought to characterize the kinetics of a single intra-articular bupivacaine injection given for postoperative analgesia, and to determine whether the technique produced toxic blood levels of bupivacaine.

Methods

Twelve healthy patients ranging in age from 17 to 67 years and undergoing arthroscopic procedures of one knee were studied. The protocol was approved by our Institutional Review Board and written informed consent was obtained from each patient. One patient was premedicated with IM midazolam 5 mg and atropine 0.4 mg, and another received IM morphine 8 mg with 0.4 mg atropine 90 minutes before surgery; the remainder of the patients received no premedication. Anesthesia was induced with thiopental and maintained with a combination of nitrous oxide and volatile anesthetic. All patients had a thigh tourniquet placed and inflated on the operative leg, with tourniquet pressures set at 250 to 400 mm Hg.

On completion of the surgical procedure, incision sites were closed and 40 ml 0.25% bupivacaine (100 mg) was injected into the articular space of the operated knee. Venous blood samples were obtained from an upper extremity no more than 30 seconds before bupivacaine injection, immediately before tourniquet release, and 5, 10, 15, 20, 30, 60, 120, 180, 240, and 300 minutes after tourniquet release. Plasma concentrations were determined by gas-liquid chro-

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Received from the Departments of Orthopedic Surgery and Anesthesiology at Northwestern University Medical Center, Chicago, Illinois. Accepted for publication April 29, 1988.

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Table 1. Demographic and Intraoperative Data

Patient no.	Age (yrs)	Sex	Height (cm)	Weight (kg)	BSA (m^2)	Tourniquet inflation time (min)*	Injection–release time (min)†
1	29	M	182.5	111.4	2.32	70	2.00
2	29	M	176.3	84.0	2.01	45	2.40
4	65	F	157.5	65.0	1.66	75	1.70
5	19	M	170.0	72.7	1.84	42	3.18
6	17	M	170.0	77.3	1.89	87	3.00
7	17	M	182.5	94.5	2.16	56	2.92
8	18	F	160.0	68.2	1.71	61	2.50
9	63	M	170.0	56.8	1.66	41	2.50
10	43	M	180.0	79.5	1.99	63	2.00
11	42	F	178.8	67.7	1.85	37	2.75
12	69	M	188.0	107.0	2.33	43	2.33
Mean	37		174.1	80.4	1.95	56	2.48
SD	20		9.6	17.5	0.23	16	0.44

*Tourniquet inflation time refers to duration of period during surgery when the tourniquet was inflated.
†Injection-release time refers to the interval between articular infusion of bupivacaine and tourniquet deflation.
Abbreviations: BSA, body surface area = 71.84 × weight(kg) × height(cm).

matography based on the technique of Mather and Tucker (4) using mepivacaine as the internal standard and with nitrogen-phosphorus detection. This method has a sensitivity of at least 0.05 μg/ml and a coefficient of variation of at most ± 5% at the plasma concentrations studied. Bupivacaine plasma concentration versus time data were analyzed by a nonlinear least squares regression technique using the SAAM 23 digital computer program developed by Berman and Weiss (5). We assumed a one compartment disposition model with an additional compartment for absorption. Thus, there are two exponential terms, with the beta phase corresponding to disposition variables. The variables determined included the volume of distribution (V_d beta), clearance (Cl), terminal half-life ($T_{½}$ beta), and the absorption rate constant (k_a). Estimated peak plasma concentrations (Cp_{max}) and time to peak (t_{max}) were calculated using the equations:

$$t_{max} = [2.3/(k_a - k_e)] (\log k_a/k_e), \text{ and}$$
$$Cp_{max} = (M_o/V_d)_e{}^{-(k_e)(t_{max})}$$

where M_o = dose, V_d = V_d beta, and k_e = the elimination rate constant (6). The relations between demographic, pharmacokinetic, and intraoperative data were examined using stepwise multiple linear regression. Criterion for rejection of the null hypothesis was $P < 0.05$. Unless otherwise stated, all data are presented as mean ± SD.

Results

Table 1 summarizes the demographic data. No adverse reactions to bupivacaine were observed. In all but one patient, samples obtained before tourniquet release had no measurable bupivacaine levels. One patient was not included in the study when technical errors prevented the plasma bupivacaine levels from being measured. On analyzing the data from the remaining 11 patients the V_d beta was 206 ± 88 L, Cl was 0.816 ± 0.378 L/min, and $T_{½}$ beta was 189 ± 84 minutes (Table 2). Cp_{max} was 0.48 ± 0.20 μg/ml and was reached in 43.4 ± 23.1 minutes after tourniquet release. A typical sample plasma bupivacaine concentration versus time curve relation is shown in Figure 1.

Multiple linear regression analysis was performed with Cp_{max} as the dependent variable. Cp_{max} had a positive relation with tourniquet time ($P = 0.02$) and a negative relation with the interval from injection to tourniquet release ($P = 0.03$). Taken together, these two factors yielded an R-square value of 0.64. The remaining variables in Table 1 did not demonstrate a significant relation to either Cp_{max} or t_{max}. In addition, there was no apparent relation between Cp_{max} or t_{max} and the presence or absence of synovitis in the knee.

Discussion

The long duration of action of bupivacaine has made it a popular choice for regional infiltration and nerve

Table 2. Pharmacokinetic Parameters in 11 Patients After Intra-articular Injection of Bupivacaine into the Knee

Patient no.	V_d (L)	Cl_e (L/min)	$T_{1/2}$ (min)	ka (min × 10^{-4})	t_{max} (min)	Cp_{max} (μg/mL)
1	223	0.438	352	11.30	36.50	0.42
2	272	0.545	346	3.70	83.17	0.31
4	188	0.790	165	7.14	42.11	0.45
5	303	1.650	126	21.70	17.42	0.30
6	100	0.461	150	4.04	50.40	0.80
7	109	0.734	103	12.70	24.40	0.78
8	122	0.541	156	9.84	32.90	0.71
9	391	1.270	212	22.40	19.18	0.24
10	203	0.939	150	5.29	50.40	0.39
11	192	1.010	131	8.31	35.36	0.43
12	165	0.595	192	2.70	85.99	0.44
Mean	206	0.816	189	9.92	43.44	0.48
SD	88	0.378	64	6.79	23.11	0.20

See text for definition of variables.

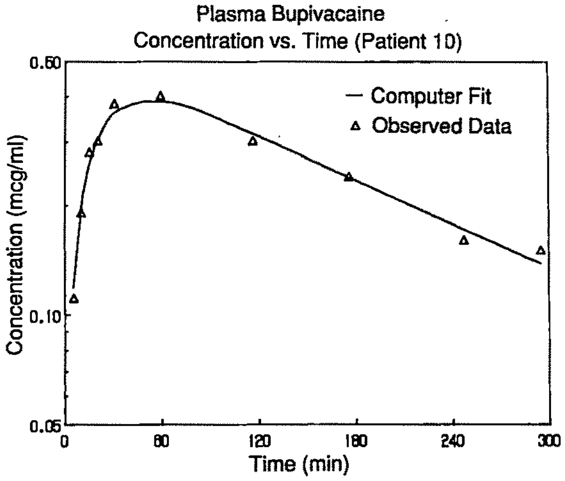

Figure 1. Sample plasma bupivacaine vs time curve, taken from patient 10 (mcg = micrograms).

blocks to relieve postoperative pain (1). Although both bupivacaine and prilocaine have been used in pressurized infusions within the knee joint to provide local anesthesia during arthroscopy (2,7), the kinetics of a single injection of bupivacaine into the intra-articular space of the knee have not been well defined.

The terminal half-life determined in the present study compared favorably to the 3.5 ± 2.0-hour half-life determined in a study in which bupivacaine was injected intravenously in three awake human subjects (8). However, the calculated clearance of 0.47 ± 0.18 L/min in these three subjects was lower than the clearance found in the present study, and the V_d beta determined from their values (V_d beta = $(T_{1/2} \times Cl_e)/0.693$) was also lower at 142 L. Our values are within 1 SD of these and thus may not be significantly different. If differences did exist, they may be due in part to a <100% bioavailability of bupivacaine in the present study, which would result in higher estimates of V_d beta and Cl. The pharmacokinetics of drugs can also be significantly altered by the concomitant administration of general anesthetics (9,10). These favorable comparisons for terminal half-life, clearance, and volume of distribution confirm the validity of our data collection and pharmacokinetic modeling.

Few studies have examined disposition of bupivacaine from the knee. Kinetic studies have been performed during continuous infusion of local anesthetic into the knee without a tourniquet (2). There is only one other study in which uptake kinetics of a single bupivacaine dose into the knee are examined. In this study by Gerber et al. (3), 20 ml 0.5% bupivacaine (100 mg) was injected into the knee in seven patients; the highest mean plasma level was 0.31 ± 0.07 μg/ml (± SE). Although this apparent peak occurred at 30 minutes, the plasma concentrations, measured in blood specimens collected only every 15 minutes, were not given a formal pharmacokinetic analysis permitting proper estimation of Cp_{max} and t_{max} values. However, their mean plasma concentrations in the 30-, 45-, and 60-minute samples did not appear to differ significantly from each other, and so are not inconsistent with our data in terms of time to peak values (3).

Absorption rates for all amide local anesthetics vary according to the site of injection in the decreasing order of intercostal, caudal, extradural, brachial plexus, and sciatic/femoral (11). In a study in which 100 mg bupivacaine was given extradurally, Cp_{max} was 0.8 μg/ml and t_{max} was 5 minutes (12), suggesting that the rate of absorption of bupivacaine from the knee joint is substantially slower than from the epidural space. Information on bupivacaine uptake from the brachial or sciatic sheath is limited, making further comparisons difficult.

The relation of higher Cp_{max} values to longer total tourniquet inflation times might be explained by the hyperemia that results from postischemic reperfusion. Such reperfusion is likely to be of longer duration with longer tourniquet times and greater buildup of products of ischemia, because it is known that a relation exists between duration of ischemia and duration of reperfusion. It has been demonstrated that the hyperemia after 1 hour of ischemia in a limb decreases by one-half after 5 minutes, but this decrease can take 25 minutes after 3 hours of ischemia (13). Also not surprising is the relation of higher Cp_{max} values to shorter time intervals between bupivacaine injection and tourniquet release. Local tissue binding of local anesthetics increases with time, so the longer bupivacaine is allowed to remain in the knee during tourniquet inflation, the slower will be the systemic absorption on return of blood flow. For this reason, one may also predict that there may be a positive correlation between the interval between bupivacaine injection and tourniquet release and duration of analgesia. This relation may be therapeutically significant and may warrant investigation.

The plasma levels of bupivacaine obtained in this study are less than the lowest levels yet recorded to have caused clinical toxicity. Previous studies examining bupivacaine toxicity after intravenous injection show that it is unlikely that levels of 3.0 μg/ml will be associated with clinical toxicity (14). Scott (15) has suggested, however, that a level as low as 2.0 μg/ml may cause toxic symptoms if the increase to this level is rapid. Also, a single case has been reported in which, after 2 hours of IV bupivacaine infusion, a bupivacaine plasma concentration of 1.1 μg/ml was associated with generalized seizures and unconsciousness in an otherwise healthy female (16). Although the levels in the present study were well below even the 1.1 μg/ml concentration, doubling of the plasma concentrations in several of our patients (as could occur after bupivacaine injection into both knees) could exceed that level and possibly result in toxicity within the first hour postoperatively.

In conclusion, this study demonstrates that intra-articular injection of bupivacaine 100 mg into the knee is a safe technique, with peak plasma concentrations occurring within the first hour after tourniquet release. Peak plasma levels can be decreased by minimizing total tourniquet inflation times and maximizing the time from bupivacaine injection to tourniquet release. These lower plasma concentrations may reflect increased local tissue binding in the knee joint and possibly increased effectiveness of the bupivacaine in providing postoperative analgesia.

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ANESTH ANALG
1988;67:876–83

SPECIAL ARTICLE

A Response Algorithm for The Low-Pressure Alarm Condition

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A response algorithm consists of a logical sequence of maneuvers to be performed in response to a specific condition. With the advent of alarm-equipped monitors that alert anesthesiologists to the presence of potentially hazardous clinical conditions, a need has arisen to develop the corresponding alarm-oriented responses expected from anesthesiologists; this problem, however, has not been satisfactorily addressed in the literature. An algorithm is proposed that guides the anesthesiologist through the three limbs of the ventilation system—gas supply system, breathing circuit, and mechanical ventilator—in response to a low-pressure alarm condition during automatic mechanical ventilation. The three-limbed algorithm rapidly and efficiently localizes the likely cause of the low-pressure condition without compromising patient safety; in the event that the search for a cause is fruitless, a default mode of ventilation is employed. A discussion is provided of common causes (e.g., disconnections), alarm-defeating circumstances (false negatives), and potential algorithm-defeating situations (multiple faults).

COMPLICATIONS—low-pressure conditions.
EQUIPMENT, CIRCUITS—low-pressures.
MONITORING—low-pressure conditions.

In the operative setting of mechanically controlled ventilation, the anesthesiologist directly assesses the adequacy of ventilation by 1) auscultation of breath sounds via a precordial or esophageal stethoscope and, by 2) observation of chest wall movement. With the advent of sophisticated monitoring instruments, the anesthesiologist routinely supplements his or her direct observation with alarm-equipped instrument monitors such as pressure/flow or CO_2 sensors. However, the exigencies of patient care may require that the anesthesiologist temporarily discontinue direct observation and rely instead on these sensors to identify inadequate ventilation. Indeed, these instrument monitors may provide earlier and more reliable detection of inadequate ventilation than do the usual direct methods.

Because of the trend toward increasing reliance by anesthesiologists on such monitors, it has become commonplace to use audible and/or visual alarms that are triggered when the sensed variable exceeds preset limits. Thus alerted to a potentially hazardous condition, the anesthesiologist is expected to rapidly and efficiently seek out and correct the problem.

With few exceptions, most current anesthesia textbooks do not address the problem of alarm-oriented responses expected from the anesthesiologist. It is proposed herein to formulate an optimal algorithm for a low-pressure alarm condition that will guide the anesthesiologist, without compromising patient safety, in performing maneuvers of maximal diagnostic merit in the least amount of time. Until recent years, anesthesia practice has been based on monitoring the patient's physiologic variables (pulse, blood pressure, respiration, skin color). With the availability of more sophisticated monitors, there is a corresponding need to develop alarm-oriented response algorithms.

Pressure alarms sense airway pressure either in the airway or elsewhere in the breathing system. Typical pressure monitors are designed to be adjustable so that the integral alarms are triggered when certain preset pressure and timing criteria are met.

Received from the Department of Anesthesiology, University of Connecticut School of Medicine, Farmington, Connecticut. Accepted for publication April 13, 1988.

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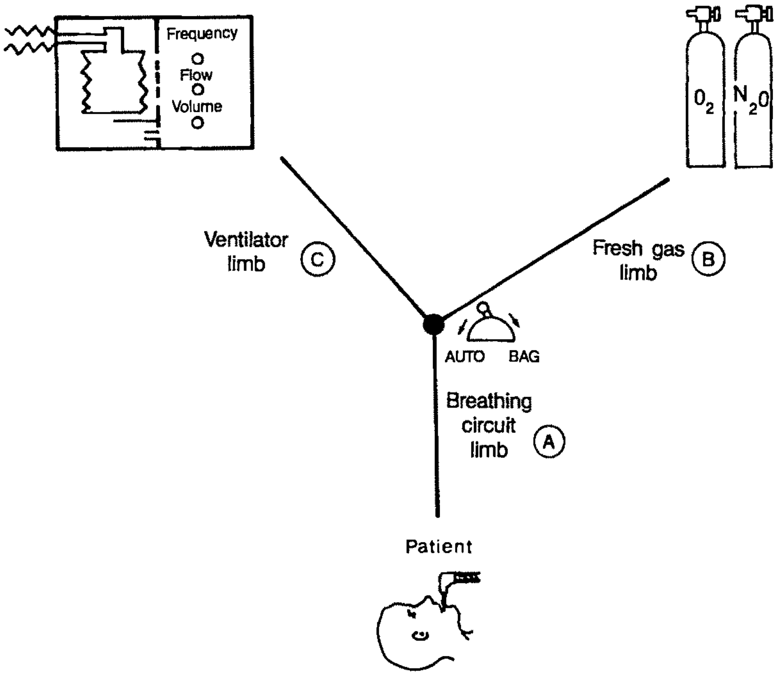

Figure 1. The three limbs of the ventilation system: (A) the breathing circuit limb, (B) the fresh gas flow limb, and (C) the ventilator limb.

For example, the Dräger DPM-S pressure monitor (1) will actuate an alarm (the low-pressure alarm) when the maximum pressure amplitude in the breathing system is less than the pressure set on the minimum ventilation pressure switch for more than 15 seconds. Late model anesthesia machines incorporate similar pressure devices, but older anesthesia machines may not. The ASA Minimal Monitoring Standards (as of October 21, 1986) state that, "When ventilation is controlled by a mechanical ventilator, there shall be in continuous use a device that is capable of detecting disconnection of components of the breathing system. The device must give an audible signal when its alarm threshold is exceeded."

Differential Diagnosis

The differential diagnosis of a low-pressure alarm condition must first be developed. In a powered mechanical ventilation system, there are three principal components: a) a gas source, b) a conducting system (or breathing circuit) and, c) a pressure generator, i.e., a mechanical ventilator. This is illustrated diagramatically in Figure 1 where the three components are seen to merge at a common point: the switchover point between mechanical and manual ventilation. In other words, the causes of low-pressure can be characterized as: a) inadequate fresh gas flow, b) a breathing system break-up or failure and, c) a faulty or poorly set mechanical ventilator. Any useful algorithm must guide the anesthesiologist through these three limbs of the overall ventilation system, taking into account the common intersection point.

Although simplified, for gases in a breathing circuit, pressure = flow × resistance. Any acute reduction in either the resistance or the flow, or in both, will cause a low-pressure state. Reductions in resistance could be caused, for example, by a disconnection or a leak that opens the circuit to the zero resistance of the environment; by inadvertent extubation or by endotracheal tube cuff deflation; and by a suction device mistakenly placed within the gas flow pathway. Reductions in flow can be caused by a reduction in the fresh gas flow; by improper settings of the ventilator (small tidal volume, very low ventilatory rate); and by an obstruction proximal to the pressure sensor.

Deferring further discussion until later, we now proceed to a presentation of the suggested algorithm (see Fig. 2).

The Algorithm: Description of Logic

If an alarm sounds, one must first scan the patient variables as reflected by the available monitors. On visual and aural identification of the alarm as the low-pressure alarm, one then proceeds to utilize the algorithm.

Evaluation of the breathing circuit. A rapid visual scan for grossly evident total disconnections in the

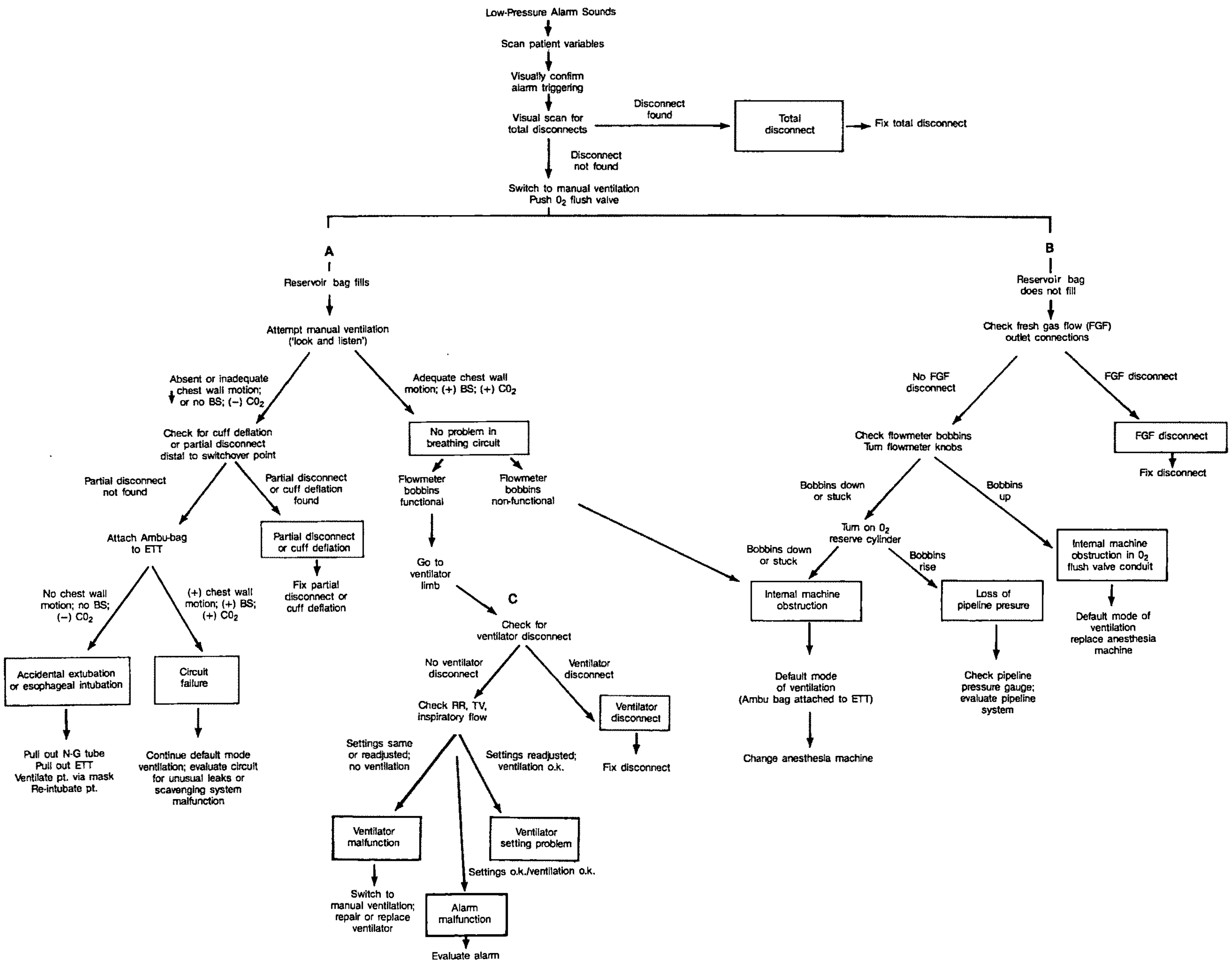
Low-Pressure Alarm Sounds
Scan patient variables
Visually confirm alarm triggering
Visual scan for total disconnects
Disconnect found
Total disconnect
Fix total disconnect
Disconnect not found
Switch to manual ventilation Push O_2 flush valve
A
Reservoir bag fills
Attempt manual ventilation ('look and listen')
Absent or inadequate chest wall motion; or no BS; (−) CO_2
Check for cuff deflation or partial disconnect distal to switchover point
Partial disconnect not found
Attach Ambu-bag to ETT
No chest wall motion; no BS; (−) CO_2
Accidental extubation or esophageal intubation
Pull out N-G tube
Pull out ETT
Ventilate pt. via mask
Re-intubate pt.
(+) chest wall motion; (+) BS; (+) CO_2
Circuit failure
Continue default mode ventilation; evaluate circuit for unusual leaks or scavenging system malfunction
Partial disconnect or cuff deflation found
Partial disconnect or cuff deflation
Fix partial disconnect or cuff deflation
Adequate chest wall motion; (+) BS; (+) CO_2
No problem in breathing circuit
Flowmeter bobbins functional
Flowmeter bobbins non-functional
Go to ventilator limb
C
Check for ventilator disconnect
No ventilator disconnect
Ventilator disconnect
Fix disconnect
Check RR, TV, inspiratory flow
Settings same or readjusted; no ventilation
Ventilator malfunction
Switch to manual ventilation; repair or replace ventilator
Settings readjusted; ventilation o.k.
Ventilator setting problem
Settings o.k./ventilation o.k.
Alarm malfunction
Evaluate alarm
B
Reservoir bag does not fill
Check fresh gas flow (FGF) outlet connections
FGF disconnect
FGF disconnect
Fix disconnect
No FGF disconnect
Check flowmeter bobbins Turn flowmeter knobs
Bobbins down or stuck
Turn on O_2 reserve cylinder
Bobbins down or stuck
Internal machine obstruction
Default mode of ventilation (Ambu bag attached to ETT)
Change anesthesia machine
Bobbins rise
Loss of pipeline presure
Check pipeline pressure gauge; evaluate pipeline system
Bobbins up
Internal machine obstruction in O_2 flush valve conduit
Default mode of ventilation replace anesthesia machine

Figure 2. The response algorithm for a low-pressure alarm condition. The three limbs of the algorithm are: (A) the breathing circuit limb, (B) the fresh gas flow limb, and (C) the ventilator limb.

breathing circuit, beginning at the Y-piece and proceeding proximally, should be performed in a few seconds. Disconnections (2), particularly at the Y-piece, are the most frequent cause of serious patient morbidity (see Discussion). Thus, all potential disconnection sites distal to the switchover point between mechanical and manual ventilation will be quickly examined. If a total disconnection is found, the two parts are reconnected. If a total disconnection is not found, one switches over to manual ventilation rather than wait for the next mechanical breath.

The change to manual ventilation temporarily excludes ventilator-related problems from consideration (diagramatically, the ventilator limb has been eliminated from the three-limbed diagram of Figure 1). This simplifies the immediate search for the cause by restricting it to either the gas source limb or the breathing circuit limb.

One should then fill the reservoir bag with 100% O_2 using the O_2 flush valve. If the reservoir bag fills properly (A in Fig. 2), the pipeline to O_2 flush valve system must be intact. With the bag now full, manual ventilation is attempted while the anesthesiologist looks at the patient's chest and listens to the patient's breath sounds. The pressure gauge may indicate the inability to generate pressure within the circuit. If a capnograph and respirometer are available, they can be used to confirm tidal exhalation immediately after the "look and listen" maneuver.

If no breath sounds are present, if no chest wall motion occurs, or if no exhalation is evident from spirometer or capnograph, then the patient is clearly not being ventilated.

With the application of sufficient force to the reservoir bag, it may be possible to detect an audible leak resulting from a partial disconnection. If no such leak or disconnection site is apparent, the anesthesiologist must proceed promptly to physically test for a partial cuff deflation and check for loose connections at the following points: 1) endotracheal tube-adapter, 2) endotracheal tube adapter-breathing circuit, 3) mass spectrometer, end-tidal CO_2, condensor/humidifier, pressure sensor, O_2 analyzer, PEEP valve, or other add-on connections, 4) inspiratory and expiratory limb connections, 5) reservoir bag connection and, 6) CO_2 cannister connection. In an average circuit, there are approximately six connection points distal to the switchover point between mechanical and manual ventilation (Fig. 3). In addition to searching for disconnections, the anesthesiologist should examine the inspiratory and expiratory limbs for kinking of the tubing and other types of obstruction (e.g., a stuck inspiratory valve proximal to a distal pressure sensor).

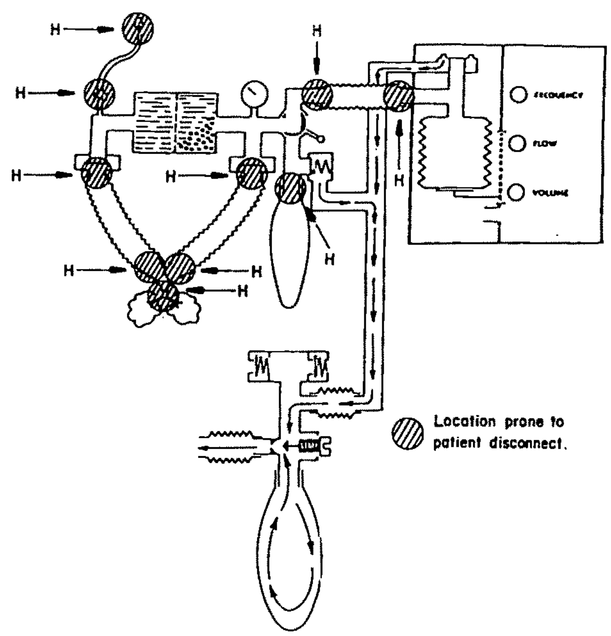

Figure 3. Connecting points with a potential for disconnections in a breathing system. (Reproduced from *Safety Guidelines for Anesthesia Systems*, with permission of P. Schreiber.)

If the search for a cuff deflation or a partial disconnection or leak is fruitless, and if manual ventilation is ineffective, it is necessary that the anesthesiologist resort to the *default mode of ventilation*: manual ventilation with a resuscitation bag (e.g., Ambu-bag) using cylinder-supplied 100% O_2. If patient ventilation still does not occur with the use of the resuscitation bag, the problem is with the location of the endotracheal tube (3) or with a defective cuff. Therefore, quickly remove any present nasogastric or orogastric tube to see if this makes a difference. If not, remove the endotracheal tube, mask ventilate with 100% O_2, and reintubate the patient.

The reason for the removal of the nasogastric tube is that it could have been mistakenly inserted into the trachea alongside the endotracheal tube and, with sufficient suction force, could be generating a low-pressure condition. Furthermore, if mask ventilation is ultimately required, the nasogastric tube could interfere with obtaining a satisfactory mask seal.

On the other hand, if switching to the default mode of ventilation with a manual resuscitation bag results in satisfactory ventilation (good breath sounds and chest wall motion plus a positive CO_2 trace), then the problem must reside within the breathing circuit. Having previously excluded a partial disconnection or an accidental cuff deflation as the cause of the circuit failure, one must now consider unusual leaks in the circuit or a possible malfunction of the scavenging system (to be discussed later).

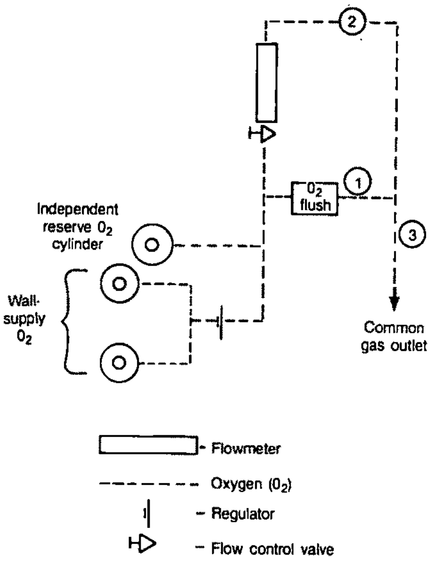

Figure 4. The oxygen supply pathway. Numbered are 1) the O_2 flush tubing, 2) the flowmeter tubing, and 3) the common gas outlet tubing.

Let us return now to the situation in which switching to manual ventilation via a circuit mounted reservoir bag results in chest wall motion, positive breath sounds, and a positive capnograph trace. This means that the breathing circuit is intact, and that the low-pressure problem must arise within either the fresh gas flow limb or the mechanical ventilator limb. If the flowmeter bobbins are functional, one concludes that the fresh gas flow limb is operative unless there is a leak between the flowmeters and the fresh gas outlet. The latter may be audibly detected when the O_2 flush valve is activated. If the flowmeter bobbins are functional, and if no gross leak is heard on use of the O_2 flush valve, proceed directly to evaluate the ventilator limb. However, if the flowmeter bobbins are nonfunctional (down or stuck), an internal machine obstruction exists that impairs fresh gas flow. The appropriate response is to initiate the default mode of ventilation with the manual ventilation bag attached to tubing connected to an O_2 cylinder via an independent flowmeter, and to replace the anesthesia machine.

Evaluation of the fresh gas supply limb. Let us return to the situation in which the reservoir bag does *not* fill using the O_2 flush valve (B in Fig. 2). When this is the case, there are three main causes: 1) a fresh gas flow disconnection, 2) an internal machine obstruction and, 3) a loss or reduction of pipeline pressure. Figure 4 illustrates the different parts of the O_2 supply system pathway.

The subalgorithm for the fresh gas limb begins with a visual check of the two fresh gas outlet connections (one connected to the anesthesia machine, the other to the breathing circuit). If no total fresh gas flow disconnection or occlusion is apparent, the actual fresh gas outlet connections should be physically reattached to avoid missing a partial disconnection, and the tubing between them should be checked for evidence of obstruction.

The flowmeter bobbins should be checked next to see if they are floating. If low flows are being used, the respective gas flow knobs should be turned to higher levels. If the bobbins do not float or do not change their positions despite knob readjustments, an O_2 reserve cylinder should be turned on immediately.

If loss of the pipeline pressure is the problem, the corresponding source pressure alarm will sound and the flowmeter bobbins will be down; in this case, the problem is temporarily corrected by turning on an O_2 reserve cylinder, which should result in the bobbins returning to their normal position. This, of course, necessitates further evaluation of the pipeline pressure system (pressure gauge, gas hoses, and wall supply).

On the other hand, if the flowmeter bobbins are still down despite turning on the O_2 cylinder, an internal machine obstruction must be present (otherwise, restoration of pressure would have sufficed to correct the problem). Once again, the *default mode of ventilation*—a manual resuscitation bag attached to tubing connected to an O_2 cylinder via an independent flowmeter—must be used while the machine is being replaced.

Rarely, the reverse situation may be encountered in which the bobbins float and the O_2 flush valve is ineffective in filling the reservoir bag. Although this would not ordinarily set off the low-pressure alarm, in this instance one must assume that there is an internal machine obstruction in the tubing leading to the O_2 flush valve (see Fig. 4). Regardless of whether the internal machine obstruction is in the flowmeter conduit or in the O_2 flush valve conduit, the response in both cases is the same: switch to the default mode of ventilation and replace the anesthesia machine.

Evaluation of the ventilator limb. If no evidence of malfunction is found within the breathing circuit limb or the fresh gas limb, the low-pressure problem must arise in the one remaining unevaluated limb: the ventilator limb. While still manually ventilating the patient, one needs to do the following (C in Fig. 2): a) check for a ventilator disconnection (two locations), b) check tidal volume and ventilatory rate and, c) adjust the inspiratory flow. After making these adjustments, reconnect the patient to the ventilator.

If an adjustable relief (popoff) valve is being used, it should be completely closed and the ventilator hose should be attached to the anesthesia machine. In the case of an automatic selector valve that excludes the popoff valve from the system during mechanical ventilation, the selector valve should be in the appropriate "ventilator" position and not in the "bag" position, which is intended for manual ventilation; in the latter case, the ventilator will operate uselessly against a completely shut valve.

After the ventilator is switched on, failure to cycle means that the driving gas supply to the ventilator has been shut off, or that the ventilator electrical power has failed. In this case, assuming that the ventilator rate setting has not been set equal to zero, the ventilator will need to be replaced.

If the ventilator cycles but the bellows shows little or no movement, a significant leak is probably present between the bellows assembly and its housing, or an obstruction may be present. If the ventilator cycles properly but does not reach its final inspiratory stop, or if the bellows does not expand completely, suspect that either the fresh gas flow setting or the inspiratory flow setting is too low; another possible cause is a leak in the anesthesia breathing system. If increasing the fresh gas flow and inspiratory flow settings fails to correct the problem, and if no immediately correctable leak is evident, the ventilator must be replaced.

If, however, all the ventilator settings are properly set, and the ventilator appears to be functioning properly, one must consider pressure-alarm malfunction (a false-positive condition).

Finally, it should be noted that different types of ventilators will respond differently in the event of a disconnection. A ventilator with a descending bellows (descent during exhalation) will continue its up and down movement by entraining ambient air into the system at the site of the disconnection. On the other hand, an ascending bellows (ascent during exhalation) will collapse in the event of a disconnection.

Scavenging System Malfunction. If an adjustable relief (popoff) valve is being used, one needs to consider the situation in which the reservoir bag fills on using the O_2 flush valve, but then collapses immediately. In some scavenging systems, wall suction is often applied both at the popoff valve and at an air intake valve. If the air intake valve is blocked (4), the suction will be applied exclusively at the popoff valve and, depending on the valve type, may cause the collapse of the reservoir bag. Hence, the air intake site along with the rest of the scavenging system should be examined. If the cause is not apparent, the scavenger suction line should be disconnected from the popoff valve. If this fails to relieve the problem, a switch to the default mode of ventilation is required until the scavenging system is fixed.

Default mode of ventilation. Impending respiratory failure can be detected with a pulse oximeter. Although the declining O_2 saturation is a late indicator of a breathing system malfunction, it is the common final pathway toward an adverse outcome. Hence, if the oximeter indicates significant O_2 desaturation, or if the patient deteriorates at any time during the performance of the algorithm, the anesthesiologist *must* switch immediately to the *default mode of manual resuscitation bag ventilation* with 100% O_2. According to Dorsch and Dorsch (5), no more than 1 minute should be spent trying to diagnose or correct the problem. As discussed earlier, it is possible for even this default mode to be ineffective in the case of an inadvertant extubation, esophageal intubation, or cuff leaf, and will require mask ventilation and possible reintubation. It is mandatory that a manual resuscitation bag be readily available in every operating program for this purpose. The gas for the resuscitation bag should come, in order of preference, from a) cylinder-supplied 100% O_2, especially during the trouble shooting phase, b) from anesthetic-containing fresh gas flow, if available, when a longer correction time is required and, c) ambient air which, if used for a few minutes, should prevent adverse consequences.

Discussion

Low-Pressure Alarm

The low-pressure alarm is intended, in part, to help indirectly to detect a disconnection in the breathing system. Should the anesthesiologist fail to detect the disconnection by the direct means noted earlier (breath sounds, chest wall movement, etc.), the resulting decrease in breathing system pressure will generally trigger the alarm, but circumstances may arise that fool the alarm, as discussed later. Although the pressure monitor is designed to detect a disconnection (the separation of two components in the breathing system), it is not designed to detect misconnections (6) (incorrect hookups between components) or all types of occlusions (obstructions that prevent circuit flow). Indeed, there are certain types of disconnections that the pressure monitor may not detect. The best example of this is a disconnection at the fresh gas flow inlet (7,8) of the anesthesia machine. Because ambient gas will be entrained by the ventilator instead of the usual fresh gas, the breathing system pressure may be maintained so that the alarm is not triggered (9). An oxygen analyzer, however, will detect the disconnection at the fresh gas flow inlet.

Location of Pressure Sensor.

The location of the pressure sensor will affect its diagnostic utility (5). Ideally, the pressure sensor should be located near the Y-piece attaching to the endotracheal tube so as to sense, in the immediate vicinity of the patient's airway, a reduction or absence of pressure changes. Practically, however, problems arise with such a location owing to buildup of condensation and risks of contamination from nearby secretions.

Faced with these problems, manufacturers have moved the pressure sensor to other locations in the breathing system, either within the ventilator itself or outside the ventilator but upstream of the breathing system inspiratory valve. The former intraventilator location is insensitive to devices that employ manual–automatic selector valves, whereas the latter external location minimizes the condensation and contamination risks but at the potential expense of insensitivity to certain conditions. Indeed, if the pressure sensor is not near the endotracheal tube, the pressure device may fail to detect a disconnection, thereby creating a false-negative condition.

False Negatives.

The most common cause of false negatives may be the failure of the anesthesiologist to preset the minimum monitoring pressure threshold. If the monitoring pressure threshold is set too low, say, below 7–8 cm H_2O pressure, the alarm will be defeated in the case of a partial disconnect and will not respond to a low circuit pressure that is still above the alarm threshold setting (10,11). Thus, it should be considered optimal practice to preset the monitoring pressure threshold as close below the peak pressure as possible.

It is useful to consider what happens when the pressure sensor is placed proximal to the inspiratory valve. Obstruction in the inspiratory limb will cause a low-pressure state distal to the obstruction, and a high-pressure state proximal to the obstruction. Because of location of the sensor, the distally lowered pressure may not be immediately detected.

False negatives may also arise a) if the local circuit resistance to flow is high so that sufficient back pressure is generated upstream to prevent sensor triggering; this can occur if the endotracheal tube is disconnected from a 15-mm connector which, because of its intrinsically high flow resistance, can produce a false indication of ventilation to the monitor; b) if a partial or total disconnection occurs, the presence of bedding sheets and pads (10) about the disconnection site may lead to sufficiently high pressures to prevent alarm triggering, and c) if a downwards bellows (which exhibits downwards descent during exhalation) is used, the bellows will continue its cyclic motion despite a patient disconnection.

Other causes of false negatives have been reported. Sarnquist and Demas (12) reported failure of a timer valve in a Ventimeter Controller that resulted in cessation of ventilator cycling, with the bellows staying in the fully extended position; because no pressure loss occurred, the disconnection alarm did not sound. Heard and Munson (13) described a scavenging system malfunction which, through a communication between the driving gas and the scavenging gas circuits, resulted in a negative pressure being applied outside the bellows thereby preventing its collapse and triggering of the alarm.

It must be understood that a low-pressure alarm is not a disconnection alarm although when used in conjunction with other alarms (capnography, spirometry) and clinical observation, it may be of help in warning of disconnections.

Disconnections

In the typical anesthesia breathing circuit, there are approximately ten potential sites for disconnection (Fig. 3) (5). However, the most likely site for a disconnection is at the connection between the endotracheal tube connector and either the elbow or the Y-adapter. About 70% of disconnections occur at this site, according to unpublished data quoted by Cooper in a study of 110 disconnections. Other disconnection sites included: seven (6%) at the common gas outlet of the anesthesia machine; 7 (6%) at one of the two connections of the ventilator to the breathing system; and 16 (21%) at various other locations, in 13 of which the site was unreported.

In an investigation of anesthesia mishaps, Cooper et al. (2) cited disconnections of the patient from the machine as being responsible for 7.5% (27 of 359) of the critical incidents involving human error or equipment failure. Other critical incident studies (14–16) have likewise resulted in comparable percentages (5 to 9%) for breathing system disconnections. All such studies have concluded that disconnections are either the first or the second most frequent potential catastrophic event during anesthesia. An excellent comprehensive review of the etiology and prevention of disconnections can be found in the Arthur D. Little, Inc study (16) conducted principally by J.B. Cooper and L.A. Couvillon.

Nature of the Algorithm: Faults and Non-Uniqueness

The algorithm has been structured so that visual maneuvers can be performed initially as a scanning mechanism, which are then followed by the more detailed hands-on testing of the actual physical components, within each of the three limbs. In terms of the time required, the early key evaluative steps in the breathing circuit and fresh gas supply limbs should take less than 1 minute, which is within the operative limit recommended by Dorsch and Dorsch.

The three-limbed algorithm is structured on a single-fault basis. It presumes that the cause of the low-pressure alarm condition can be localized to one of the three limbs, identified, and ultimately corrected. In the case of multiple simultaneously occurring faults, the algorithm may be rendered less effective as a diagnostic aid. Nonetheless, a careful systematic check-out of each limb as previously described should detect the multiple errors even under these unusual circumstances. During use of the algorithm, the pulse oximeter should be used at each decision point to determine if the alternate mode of manual resuscitation bag ventilation should be instituted immediately. As before, the prescribed default mode of ventilation with a manual resuscitation bag is employed if the algorithm fails to reveal the underlying problem.

It should be pointed out that, in view of the variety and complexity of modern anesthesia equipment, no single algorithm can hope to cover all possible complications. However, it is appropriate to formulate a general response plan to the low-pressure alarm condition; this response algorithm can then be modified to take into account the specific characteristics of the anesthesia breathing system in use. In this respect, the proposed algorithm is not unique. Nonetheless, we believe that it serves as a valuable heuristic aid for the development of troubleshooting skills in the operative setting.

We would like to acknowledge useful discussions with Dr. Ralph Epstein and Dr. Peter Fletcher. We also appreciate the constructive comments made by Mr. Peter Schreiber of North American Drager. The typing assistance of Mrs. Dorothy Maguire is appreciated.

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TECHNICAL COMMUNICATIONS

Ventilatory Frequency Influences Accuracy of End-Tidal CO_2 Measurements

Analysis of Seven Capnometers

Robert P. From, DO, and Franklin L. Scamman, MD

An accurate high-frequency response is mandatory when end-tidal CO_2 (PET_{CO_2}) is monitored during pediatric general anesthesia. The purpose of this study was to assess the accuracy of six infrared-based capnometers and one multiplexed mass spectrometer available at our institution at increasing frequency. Capnometers studied were the Datascope Accucap, Hewlett-Packard 47210A capnometer, Narkomed 3 Capnomed, Novametrix Capnogard model 1250, Perkin-Elmer Advantage, Puritan-Bennett Datex CO_2 monitor, and Traverse Medical Monitor model 2200 capnometer. Changes in CO_2 concentration were generated by a solenoid valve switching between 100% O_2 and 7% CO_2 in O_2. Frequencies, 8–101 cycles/min were chosen to stimulate a range that might be generated by children during general endotracheal anesthesia. At every rate the displayed PET_{CO_2} was recorded. Differences in displayed PET_{CO_2} from known CO_2 ranged from -16.4 to $+6.6$. At or below frequencies of 31 cycles/min, four capnometers overreported and three underreported PET_{CO_2}. At frequencies above 31 cycles/min, six capnometers underreported and one overreported PET_{CO_2}. Errors may be clinically significant if they influence ventilator settings for patients.

Key Words: EQUIPMENT—capnometers. Monitoring—capnometry. MEASUREMENT TECHNIQUES—capnometry. CARBON DIOXIDE—measurement.

An accurate high-frequency response is mandatory when end-tidal CO_2 (PET_{CO_2}) is monitored during pediatric general anesthesia (1). The frequency at which a multiplexed mass spectrometer (Perkin-Elmer Advantage) can accurately measure PET_{CO_2} has been evaluated (2). The effect of frequency on infrared-based capnometers has not been evaluated. The purpose of this study was to assess the accuracy of PET_{CO_2} measurements at increasing frequency of six infrared capnometers and compare these devices to the mass spectrometer.

Methods

Capnometers studied were the Datascope Accucap (Datascope Corp., Paramus, NJ), Hewlett-Packard 47210A capnometer (Hewlett-Packard Company, Waltham, MA), Narkomed 3 Capnomed (North American Drager, Telford, PA), Novametrix Capnogard model 1250 (Novametrix Medical Systems Inc., Wallingford, CT), Perkin-Elmer Advantage (Perkin-Elmer, Pomona, CA), Puritan-Bennett Datex CO_2 monitor (Puritan-Bennett, Lenexa, KS), and Traverse Medical Monitor model 2200 capnometer (Sensors, Inc., Saline, MI). All machines were given the warm-up period suggested by their manufacturer and were then calibrated if possible. Some had no external calibration adjustment. Sample flow rates (50–300 ml/min) were set for pediatric applications. The Datascope Accucap, Puritan-Bennitt Datex CO_2 monitor, Novametrix Capnogard, and Traverse capnometer have adjustable sample flow rate settings but were maintained at pediatric rates during the study. The sampling catheters used were those supplied with the machine. All were less than 3 m long except for the Perkin-Elmer Advantage, which had a 50-m catheter. The Hewlett-Packard 47210A capnometer sam-

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Received from the Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa. Accepted for publication March 2, 1988.

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TABLE 1. Amount of error in End-Tidal CO_2 Measurements in Seven Capnometers

Frequency (cycles/min)	Datascope Accucap	Hewlett-Packard 47210A	Narkomed 3 Capnomed	Novametrix Capnogard model 1250	Perkin-Elmer Advantage mass spectrometer	Puritain-Bennett Datex CO_2 monitor	Traverse Medical Monitor model 2200
8	+6.6	+1.6	+2.6	+6.6	−2.4	−1.4	−5.4
16	+5.6	+1.6	+1.6	+4.6	−2.4	−1.4	−5.4
31	+3.6	+0.6	+1.6	+4.6	−3.4	−1.4	−5.4
53	−0.4	−0.6	−0.6	+4.6	−4.4	−2.4	−5.4
72	−3.4	−0.6	−1.4	−2.4	−6.4	−3.4	−6.4
84	−5.4	−0.4	−1.4	+2.6*	−8.4	−5.4	−16.4*
101	−7.4	−1.4	−3.4	+1.6*	−11.4	−7.4	−5.4*

Results are reported as the observed value minus the true value for CO_2 (51.4 mm Hg).
*These values are suspect because the capnometer could not reliably detect respiratory rate at these frequencies.

pled directly from a mainstream chamber. The sampling catheters of the six remaining capnometers were all inserted into a common sampling point with a continuous outflow of 6 L/min. Changes in CO_2 concentration were generated by a solenoid valve (Humphrey 062E1) driven from 8 to 101 cycles/min, switching between 100% O_2, simulating inspiration, and O_2 with 6.94% CO_2 (barometric pressure 737 mm Hg, CO_2 51.4 mm Hg), simulating expiration. The inspiratory/expiratory (I:E) ratio was fixed at 1:2. Frequencies were chosen to simulate a range that might be generated by children during general endotracheal anesthesia. At every rate the displayed value of PET_{CO_2} was recorded. Also recorded, when available, were the displayed values for frequency and inspired CO_2.

Results

Data from each capnometer studied are shown in Table 1. Error is reported as the observed value minus the true value (51.4 mm Hg). Differences in displayed PET_{CO_2} from CO_2 ranged from −16.4 to +6.6 for the population of capnometers studied. At or below frequencies of 31 cycles/min, four capnometers overreported and three underreported PET_{CO_2}. Six capnometers underreported and one overreported PET_{CO_2} at frequencies above 31 cycles/min. The Novametrix Capnogard reported high values except at a frequency of 72 cycles/min, where it also underreported. The Perkin-Elmer Advantage and the traverse capnometer had the most error; the Hewlett-Packard 47201A capnometer had the least. The Novametrix Capnogard and the Traverse capnometer were unable to determine rate at frequencies above 84 cycles/min. The Datascope Accucap, Hewlett-Packard 47210A and Perkin-Elmer Advantage determined ventilatory rate with an accuracy of ± 1/min of the actual rate. Indicated inspired CO_2 ranged from 0 to 28 mm Hg.

Discussion

Factors known to affect PET_{CO_2} measurements include expiratory flow, concentration profiles, sample flow rate, and sample tube dimensions or material (2–4). Investigations have been performed regarding sampling site, circuit configuration, or minute ventilation (5–9). In vitro studies have been performed with constant sample flow, with nonpulsatile flow, or with ventilatory frequency adjusted for calculated eucapnia (3,6,9). In vivo studies have adjusted minute ventilation to maintain eucapnia (5,7–9). Ventilatory frequency has been adjusted, but with only one type of commercially available sampling system (2,3).

The physical arrangement of the sampling configuration in this study optimized the opportunity for a good high-frequency response. In in vivo configurations, the opportunity is certainly less (5–8). Our data indicate that when conditions are standardized for all variables except frequency, the capnometers studied did not display the true CO_2. At or below 31 cycles/min, four capnometers displayed high values, and three displayed low values. Causes of error in this range include inaccurate calibration and/or inadequate inspiratory/expiratory (peak and valley) determination. Above 31 cycles/min, six of seven capnometers tested consistently underreported PET_{CO_2}. The genesis of underreporting error is thought to be the "mixing" of adjacent breaths during transport down the sampling catheter and in the analysis chamber. The Perkin-Elmer Advantage (multiplexed mass spectrometer) and the Traverse capnometer appear to be the most sensitive to the mixing effect. The long sampling catheter of the multiplexed system (50 m) presumably contributes to the error; the Hewlett-Packard 47210A is least sensitive, presumably because it has no sampling catheter but has an in-line analysis chamber.

Error in PET_{CO_2} measurements during this study ranged from −16.4 to +6.6, values that may be clinically significant if used to adjust ventilator settings for patients. Because it is possible for the respiratory rate of a child under halothane anesthesia to exceed 60 breaths/min and therefore generate gas-concentration changes of twice that frequency, and because all capnometers tested underestimated PET_{CO_2} at frequencies in this range, PET_{CO_2} values should be used only as an aid in adjustment of minute ventilation. PET_{CO_2} values must be interpreted with knowledge of the limitations of capnographic monitoring.

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ANESTH ANALG 1988;67:887–9

Evaluation of Helium Interference with Mass Spectrometry

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Key Words: GASES, NONANESTHETIC—helium. MEASUREMENT TECHNIQUES—mass spectrometry; helium effect.

The use of mass spectrometry for accurate and reliable measurement of respiratory gases has gained wide acceptance in clinical anesthesia. However, the addition of inert gases or gases not routinely measured by the mass spectrometer interferes with the accuracy of this instrument (1,2). Helium, an inert gas, is added to the inspired gas mixture by some clinicians during laryngotracheal laser surgery and during the ventilation of patients with fixed airway obstruction (3,4). Already, two cases have been reported in which helium interfered with the ability of a mass spectrometer to accurately determine other gas concentrations (5). To more completely define this effect, values for CO_2 and O_2, determined by infrared and polarographic means, respectively, were compared with those determined by mass spectrometric analysis of gases that did or did not contain helium.

Methods

A test lung, into which CO_2 was infused at 200 ml/min to simulate the lungs of an adult patient, was mechanically ventilated by an anesthesia machine with a standard circle system and an Ohio 7000 electronic ventilator. Airway gases were monitored with a Perkin-Elmer MGA 1100 mass spectrometer, a SARAcap analyzer (polarographic O_2 and infrared CO_2), a Datascope Accucap analyzer (polarographic O_2 and infrared CO_2), and an Ohmeda 5100 analyzer (polarographic O_2). The sidestream analyzers (the mass spectrometer, the SARAcap, and the Datascope Accucap) sampled gases from the end of an endotracheal tube attached to the mechanical lung (Fig. 1). The Ohmeda 5100 analyzer was an in-line monitor in the anesthesia circle system.

Three series of measurements of O_2 in the inspired gases and CO_2 in the expired gases were made with each of five different inspired gas mixtures. Two control runs were performed, the first with inspired concentrations of 100% O_2 and the second with 50% O_2 and 50% N_2O. Three concentrations of helium were then added to O_2: 75% O_2 with 25% helium, 50% O_2 with 50% helium, or 40% O_2 with 60% helium.

All measurements were made after equilibration. The respiratory rate was maintained at 10 breaths/min with a constant minute ventilation determined by a spirometer in the expiratory limb and a total fresh gas flow of 4 L/min. Statistical analysis was performed using analysis of variance, a difference of $P < 0.001$ being considered statistically significant.

Results

The results are summarized in Figures 2 and 3. There were no significant differences between the monitors in reported values of inspired O_2 or expired CO_2 during control runs with either 100% inspired O_2 or 50% O_2 and 50% N_2O. However, the addition of helium had a marked and consistent effect on both inspired O_2 (Fig. 2) and expired CO_2 (Fig. 3) values reported by the mass spectrometer. The presence of helium consistently resulted in overestimation of the actual values of O_2 and CO_2 when compared with the values reported by the other gas monitors. At inspired concentrations of helium >50%, the mass spectrometer alarmed and reported "line blocked." No data were reported by the mass spectrometer until the helium concentration was lowered to 50% of the inspired gas mixture. Measurements of gases by the other mass spectrometer terminals in our multiple sampling system remained unaffected and accurate during the brief periods of testing with helium. Finally, the polarographic O_2 and infrared CO_2 determinations were not affected by helium (Figs. 2 and 3).

Received from the Departments of Anesthesiology and Neurosurgery, University of Florida College of Medicine, Gainesville, Florida. Accepted for publication April 8, 1988.

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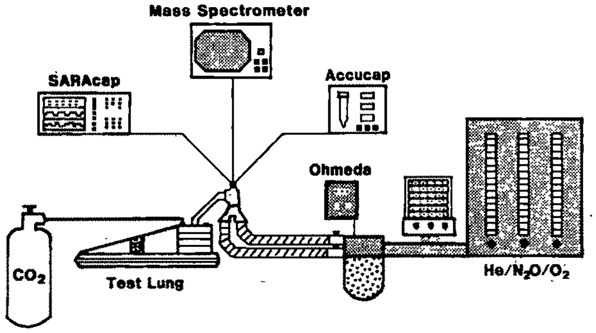

Figure 1. Experimental setup of sidestream analyzers (mass spectrometer, SARAcap, Datascope Accucap), Ohmeda 5100 analyzer, test lung, and anesthesia machine.

Discussion

Mass spectrometry is extremely valuable for monitoring patients during the intraoperative period. It has a wide range of applications, such as for verification of adequate denitrogenation during preoxygenation ($FeN_2 < 0.10$), for verification of tracheal intubation, and for measuring gas values to quantify the adequacy of O_2 delivery, soda lime, inspiratory/expiratory valve function, and appropriate concentrations of anesthetic.

Although seven gases can be measured simultaneously (O_2, CO_2, N_2O, N_2, halothane, enflurane, and isoflurane), other gases that are occasionally added to the inspired mixture, such as aerosolized propellants found in inhaled bronchodilators, may be mismeasured (1,2), and inert gases such as helium and water vapor are unmeasured. The presence of mismeasured and/or unmeasured gases prevents accurate measurement of the gases for which the mass spectrometer is designed.

An explanation for this phenomenon can be extrapolated from the basic operating principle of the magnetic sector mass spectrometer (6). Under standard operating conditions, a portion of the gas sample is ionized and accelerated into a magnetic field. The ions are diverted into circular paths, the radii of which are determined by the charge-to-mass ratio of each particle. The ions strike specifically positioned collector plates, where specified ions are known to impact and the instrument counts the "hits." The total number of hits is assumed to constitute 100% of the gas sample. This information is translated into a mass spectrum that is analyzed to determine both composition and relative concentrations of the gases in the sample (6). The trajectories of helium molecules do not terminate on a collector plate and, thus, are not recorded as hits. Therefore, they constitute an unmeasured fraction of the total gas sample because they are unrecognized by the mass spectrometer. Instead, the mass spectrometer assumes, according to its algorithm, that the total number of hits is representative of the entire gas sample. For example, in the inspired gas mixture of 50% O_2 and 50% helium, the mass spectrometer recorded only hits by ionized O_2 particles and reported that >96% of the sample was O_2. When an inspired gas mixture with >50% helium was tested, the mass spectrometer reported "line blocked" repeatedly. This is an internal alarm, which signifies that an insufficient sample reached the analyzing chamber. This results from the instrument attempting to scale up the signals from the collective hits of the other gases. Because the mass spectrometer is unable to more than double the gain, i.e., to scale up a sample that represents <50% of the total gas particles up to 100%, an insufficient quantity of sample is sensed and a "line blocked" alarm is reported.

This attempt to scale up measured gases when unmeasured gases are present is demonstrated by the inappropriately high values reported for inspired O_2 and expired CO_2 when helium was added. Clinically, these inaccurate measurements of inspired O_2 could falsely inform the anesthesiologist that adequate O_2 was being delivered to the patient and that ventilation was inadequate because of the elevated CO_2 measurement.

Some propellants, unlike helium, interact with the ion detectors and thereby cause the apparent appearance of additional measured gas (i.e., one for which a collector[s] exists). When aerosolized bronchodilators are administered during the use of isoflurane, the propellant particles strike the isoflurane collector plate and are interpreted as isoflurane gas. Thus, the reported concentration of isoflurane is falsely elevated (1).

In summary, while helium has a marked, quantifiable effect on both inspired O_2 and expired CO_2 values reported by the Perkin-Elmer MGA 1100 mass spectrometer, it does not affect either polarographic O_2 or infrared CO_2 measurements.

Intelligent use and obtainment of accurate information with any instrument requires that it be used within its design limitations. The mass spectrometer, as currently designed, should not be used when helium is in the respired gas mixture. Instead, when helium is in use, either a mass spectrometer modified to measure helium, or gas analyzers, which are unaffected by helium (e.g., polarographic O_2 and infrared CO_2), should be used rather than a regular, clinical mass spectrometer.

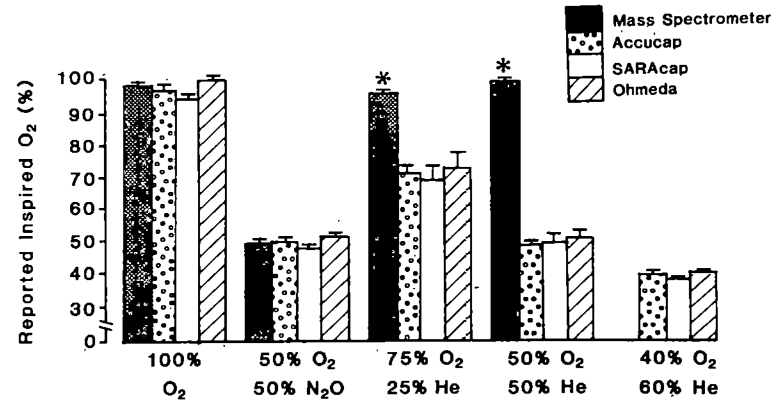

Figure 2. Values are means ± SD. $^*P < 0.001$. Reported inspired oxygen (%) by the mass spectrometer and by the Datascope Accucap, SARAcap, and Ohmeda 5100 analyzers during ventilation with oxygen (O_2), nitrous oxide (N_2O), and helium (He) in various combinations. No data were available from the mass spectrometer when the 40% O_2/60% He mixture was used.

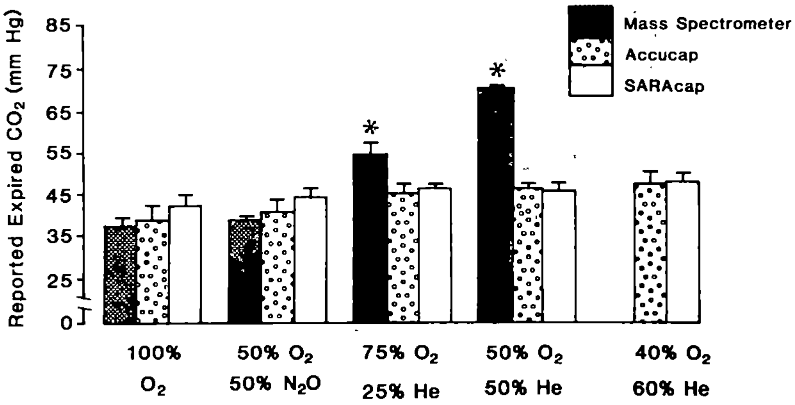

Figure 3. Values are means ± SD. $^*P < 0.001$. Reported expired CO_2 partial pressure (mm Hg) by the mass spectrometer and by the Datascope Accucap and SARAcap analyzers during ventilation with oxygen (O_2), nitrous oxide (N_2O), and helium (He) in various combinations. No data were available from the mass spectrometer when the 40% O_2/60% He mixture was used.

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Clinical Reports

Detection of Perioperative Myocardial Ischemia Using Holter Monitoring with Real-time ST Segment Analysis

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Key Words: HOLTER MONITOR, ISCHEMIA DETECTION—real-time ECG analysis.

Perioperative myocardial ischemia and infarction remain the leading cause of morbidity and mortality in patients undergoing major vascular surgery (1,2). Many techniques for the diagnosis of ischemia have been described. Implicit in this effort is the assumption that early detection and treatment will improve outcome. We report a case of a patient who underwent a carotid bypass procedure in whom the use of a Holter-monitor, Monitor One Star (QMEDInc., Clark, NJ), with real-time ST segment analysis capabilities facilitated early detection and treatment of myocardial ischemia.

Case Report

The patient was a 61-year-old woman suffering from right-hemispheric transient ischemic attacks who was scheduled for a right subclavian to common carotid artery bypass graft. Pertinent medical history included severe coronary artery disease, necessitating a two-vessel coronary artery bypass graft 12 years earlier, a subendocardial myocardial infarction (MI) 6 months earlier, and intermittent angina at rest during the current hospitalization. She also suffered from diabetes mellitus and severe hypertension, with a systolic blood pressure (BP) ranging from 150-210 mmHg. Invasive cardiac evaluation, including catheterization, was refused by the patient. She was treated with nitroglycerin (TNG) 10 mg every 6 hours, propranolol 40 mg every 8 hours, nifedipine 30 mg every 4 hours, clonidine 0.2 mg twice daily, captopril 12.5 mg every 8 hours, hydrochlorothiazide 50 mg once a day, KCl, and glyburide 2.5 mg daily, all taken orally. Electrocardiogram (ECG) was significant for an old inferior MI and nonspecific ST depression in leads I, AV_L, and V_4-V_6. On the morning of the operation, the patient received all her regular medications except for hydrochlorothiazide and glyburide, and was well-sedated with oral diazepam, 10 mg. Intraoperatively, she was monitored with a pulse oximeter, an end-tidal CO_2 monitor, an arterial line, a pulmonary artery catheter and an ECG lead approximating CS_5 (negative lead-right subclavicular, positive lead-precordeal V_5). The latter was monitored on a Hewlett-Packard ECG Module (78203C) and oscilloscope (78304A). On the evening before surgery, the patient had been connected to an Avionics Model 445 Holter monitor (Del Mar Avionics, Irvine, CA) recording leads CM_2 (negative lead-manubrium, positive lead-precordial V_2) and CM_5 (negative lead-manubrium, positive lead-precordial V_5). In addition, the real-time Holter monitor (QMED) was attached in a position approximating CS_5. Given the patient's pre-existing ST depression of 1 mm, the real-time Holter was programmed to define a 2-mm depression as an ischemic event.

The patient was hemodynamically stable before induction, with a BP of 175/55 mmHg, a heart rate (HR) of 50 beats/min, and a pulmonary capillary wedge pressure (PCWP) of 7 mmHg. Anesthesia was induced with fentanyl 1.25 mg and pancuronium 10 mg was given to facilitate intubation. There was no change in hemodynamics or oxygen saturation,

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Received from the Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, New York. Accepted for publication April 4, 1988.

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which remained at 100%. An oral airway was placed; BP increased to 190/70 mmHg and HR to 80 beats/min. Within 4-minutes the real-time Holter sounded an alarm, signalling 2 mm of ST depression. At that time, there was inconclusive evidence of new ST depression on the operating room oscilloscope and the PCWP had increased from 7 to 13 mmHg. Administration of additional intravenous fentanyl (3 mg total), along with midazolam (1 mg), and nitroglycerin (up to 0.4 μg-kg^{-1}-min^{-1}) restored the hemodynamic variables to baseline values. These did not change at the time of tracheal intubation or surgical incision. Shortly thereafter, and 30 minutes after the start of the ischemic episode, the real-time Holter signalled resolution of the ST segment depression.

Subsequent intraoperative course was uneventful, with continued use of fentanyl (4 mg), 60% nitrous oxide, and infusion of TNG in amounts sufficient to maintain a systolic pressure of 140-170 mmHg (up to 2.5 μg-kg^{-1}-min^{-1} was required). No further evidence of ischemia was noted. The right carotid artery proved to be inoperable and a left carotid endarterectomy was performed. The patient remained intubated postoperatively.

Upon arrival in the intensive care unit (ICU) she was stable on 2 μg-kg^{-1}-min^{-1} of TNG with a BP of 165/50 mmHg, a HR of 60 beats/min, and a PCWP of 8 mmHg. A 12-lead ECG revealed new biphasic T waves in V_2 and V_3, without significant change in the baseline anterolateral ST depression. Thirty minutes later, the real-time Holter sounded an alarm, once again signalling ST segment depression. Review of the ECG on the ICU oscilloscope was nondiagnostic. Blood pressure had increased to 190/70 mmHg with a HR of 65 beats/min and PCWP of 15 mmHg. During the ensuing 15 minutes the real-time Holter registered progressive ST depression to a maximum of 4 mm. With fentanyl (.25 mg), IV TNG (up to 4 μg-kg^{-1}-min^{-1}), sublingual nifedipine (3 doses of 10 mg), and IV propranolol (10 mg total), there was resolution of the ST segment depression, as reflected in the ST segment histogram (Fig. 1). The total ischemic period approached 2 hrs. Subsequent serial ECGs were consistent with an anterolateral subendocardial MI. A creatinine phosphokinase (CPK) peak isoenzyme level of 456 units/L (normal less than 50 units/L) was reached 24 hours later with a 3.4% MB band. The patient was extubated on postoperative day 2 and had a subsequent course characterized by crescendo angina, ultimately necessitating emergency catheterization and coronary artery bypass surgery. She recovered uneventfully from the latter.

Discussion

Holter monitoring has been used for many years as a means of analyzing heart rhythm in ambulatory patients. Recent advances have allowed the application of this technology to analysis of the ST segment. In this instance we used an Avionics Holter recorder and Marquette series 8000/T Holter analysis system (Marquette Electronics, Milwaukee, WI). Two-channel monitors provide a continuous recording of 2 bipolar ECG leads over a 24-hour period. Lead selection is dependent on whether rhythm monitoring or ischemia detection is of primary interest. Standardization is provided by a calibration signal that defines a 10-mm deflection as equal to 1 mV. The recording is retrospectively reviewed, initially by technicians using scanning equipment with computer-assisted analysis, and ultimately by a cardiologist who visually inspects pertinent ECG segments. Current Holter reports, in addition to rhythm analysis, include a trend line that follows ST segment amplitude and slope, as well as direct printout of any pertinent ECG segments.

To maximize the detection of ischemia a bipolar modification of a true V_5 lead is usually utilized. The CM_5 and CS_5 leads employed during this case have each been shown to detect approximately 90% of the episodes of ST depression noted on simultaneous 12-lead ECG recording during treadmill exercise testing (3,4,5). With the addition of a second modified precordial lead (we used CM_2) a 96% concordance between ischemic changes noted by Holter recording and simultaneous 12-lead electrocardiography has been demonstrated (3). Further validation of the import of Holter-recorded ST segment changes is provided in a study of patients hospitalized with unstable angina. The presence of ischemic ST segment changes on a 24-hour Holter recording proved to be the most reliable single predictor of myocardial infarction within the subsequent month (6). In an earlier study, Deanfield et al. were able to correlate reversible perfusion defects on radionuclide scan and ST depression on simultaneous Holter recordings (two thirds of which were asymptomatic) (7).

A significant limitation of traditional Holter monitoring in the perioperative period is that recordings are usually analyzed and interpreted retrospectively. The real-time Holter, described in this case, not only records specific ECG segments for later playback, but also analyzes the rhythm and ST segment in real-time and alerts the user to acute perturbations. The user programs the degree of ST depression requisite to meet criteria for ischemia, usually a 1-mm change from the patient's baseline ST segment amplitude.

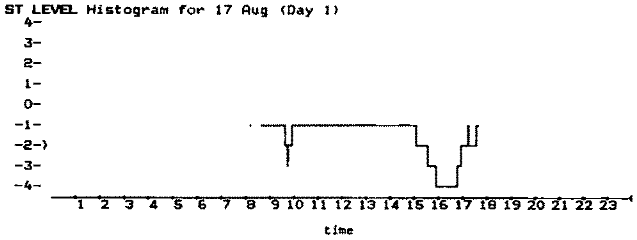

Figure 1. The ST segment trend reflects the ischemic episode at induction at 0930 and the more prolonged postoperative ischemia at 1500. The latter episode shows a maximal ST segment depression of 4 mm with ultimate return to the baseline depression of 1 mm.

The microprocessor within the Holter has been previously programmed to measure the ST segment 60 ms after the J point (where the QRS complex ends and ST begins) and to require a horizontal or downsloping ST segment depression that endures for 40 seconds before criteria for ischemia are met. The report, printed retrospectively, includes a 1-mV calibration signal, a histogram of ST segment amplitude versus time (Fig. 1), and a finite number of ECG segments representing any perturbations of ST segment or rhythm diagnosed by the monitor. Further technical details of this monitor have recently been reviewed (8).

Our case demonstrates the advantage of Holter monitoring with real-time ST segment analysis in the early recognition of perioperative ischemia. The ischemia noted on induction was accompanied by a subtle, nondiagnostic ST segment change on the operating room oscilloscope, as well as a moderate increase in PCWP without change in waveform. The increase of the latter, in the setting of a presumably increased afterload, and attended by a relatively stable ECG, would not have led to the diagnosis and treatment of ischemia without the alarming real-time Holter. Likewise, though the ECG and hemodynamic correlates of the postoperative ischemic episode were more dramatic, it is unlikely it would have been recognized expeditiously (if at all) without this new monitor. Detection of ischemia was compromised for many reasons, including transfer of care to a team less schooled in the diagnosis and management of ischemic heart disease, neglect in calibration of the ECG signal, and poor lead placement. Furthermore, accurate interpretation of the ECG ST segment on operating room or ICU monitors can be limited by phase shift and inadequate low frequency response (9). Although the ischemic episode in this patient progressed to MI, relatively early recognition and treatment may have prevented further complications.

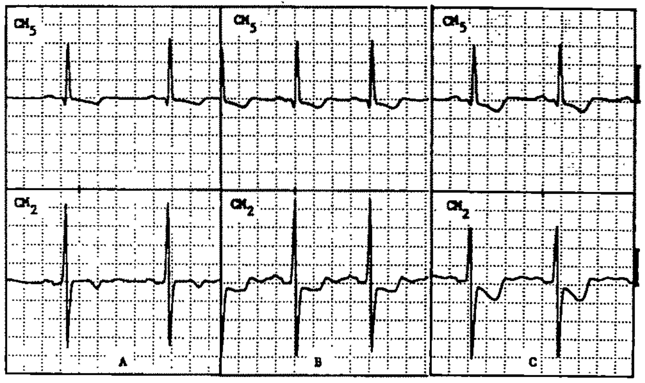

Figure 2. Simultaneous Holter (Avionics) recording corroborates the ischemia detected by the real-time Holter monitor. (A) Baseline ECG at 0610. (B) Transient ST segment depression at induction (0942). (C) Maximal degree of ST depression postoperatively (1606).

A limited body of data suggests good correlation between the real-time ischemia detection of this monitor and simultaneous ST segment changes documented on either stress test recordings or Holter systems with more extensive validation (8,10–12). Indeed, the ischemic episodes noted in this case were confirmed by retrospective review of the Avionics recording (Fig. 2). Maximal ST depression was 0.5 mm in CM_5 and 1.5 mm in CM_2, and 1.2 mm in CM_5 and 3 mm in CM_2, at induction and postoperatively, respectively. We have been satisfied with the sensitivity of this real-time monitor in the detection of ischemic ST segment change relative to simultaneous 2-channel Holter recordings. The specificity of ST segment changes diagnosed by this monitor, particularly within the operating room environment, remains to be defined. A number of false positive responses, some temporally related to cautery, have yielded a specificity of 66% in our hands.

Our limited experience, as well as the small numbers in previous studies (8,10–12), indicate the need for further data validating this technology. Similar efforts to employ real-time and computer-assisted ST segment analysis in the intraoperative setting have produced variable results in terms of sensitivity and specificity (13,14). They, too, demand larger and more comprehensive validation studies.

One limitation of this real-time Holter is the utilization of a single bipolar ECG lead. As noted earlier the addition of a second bipolar lead would further enhance ischemia detection (3,4). Another major improvement would be some sort of provision for immediate visualization of the Holter-recorded ECG at the time ischemia or arrhythmia is diagnosed. Such documentation would allow the user to screen out artifactual false positive responses immediately and provide for greater confidence in the decision to begin urgent therapy.

Accumulated data suggest that other means for detection of ischemia are more sensitive than ST segment analysis (14,15). Nevertheless, ECG monitoring remains the least expensive and least invasive, as well as the most readily available means of ischemia detection. Slogoff and Keats helped validate this endpoint by demonstrating a correlation between perioperative ST segment depression and subsequent MI (16). Given the portable nature of Holter monitoring, it seems logical to extend this type of ischemia monitoring over the entire perioperative period. A number of potential uses are suggested, including the detection and prognostic implication of preoperative ischemia. There is an apparent high incidence of the latter (16,17). Similarly, despite the awareness of the significant incidence of ischemic events for up to 3 postoperative days, the facilities for ischemia detection are not always available or adequate during this time. Lastly, despite improvements in equipment and knowledge of lead placement, it is apparent that changes in ST segment continue to go unrecognized in the operating room (18,19). Real-time ST segment analysis might limit the incidence of unrecognized ischemia and promote earlier recognition and treatment of more overt episodes.

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Effect of Horizontal Lithotomy Position on Hyperbaric Tetracaine Spinal Anesthesia

Kenneth A. Schmidt, MD, and Scott A. Snyder, MD

Key Words: ANESTHETIC TECHNIQUES—spinal.

Spinal anesthesia is often the preferred technique for transurethral resection of the prostate (TURP). It is not clear, however, how soon the patient should be placed in the lithotomy position after receiving the anesthetic. Some anesthesiologists place the patient in the horizontal lithotomy position immediately after injecting the spinal anesthetic, whereas others keep the patient in the supine horizontal position for various lengths of time until the anesthetic has become at least partially fixed. Review of the literature reveals that this issue has not been resolved. It is important to know if horizontal lithotomy position alters the level of anesthesia or hemodynamics so that anesthetic dosage and fluid therapy can be adjusted appropriately. If no difference occurs, then valuable operating room time can be saved by placing the patient in surgical position immediately after spinal injection. The present study was initiated to define whether prompt assumption of the horizontal lithotomy position, instead of delaying for 10 minutes the lithotomy position, results in clinically significant differences in anesthesia sensory level, blood pressure, or heart rate after spinal hyperbaric tetracaine injection.

Methods

Fifty patients scheduled for elective TURP were studied. Written consent was obtained for spinal anesthesia and study participation as approved by the institutional research committee. Up to 4 mg midazolam IM was given 60 minutes preoperatively for sedation.

On arrival in the operating room, the patient was placed in the supine position on the operating table. Heart rate and blood pressure were recorded. An 18-gauge intravenous cannula was inserted and 7 ml/kg of an electrolyte solution (Normosol-R) was started. The patient was then moved to a sitting position so that the buttocks would not need to be moved for surgery. After sterile preparation and injection of 1 ml 1% procaine locally, a 22-gauge spinal needle was inserted into the subarachnoid space at the L3–4 interspace. After aspirating 0.2 ml cerebrospinal fluid to confirm proper needle placement, 2 ml of anesthetic solution (1 ml 1% tetracaine mixed with 1 ml 10% dextrose in water) was injected over 6 seconds, under the supervision of one of the authors.

Patients were then randomly assigned to one of two groups. After spinal injection, patients in group A were placed immediately in the supine, horizontal position for 10 minutes and then placed into the horizontal lithotomy position. Patients in group B were assisted immediately from sitting to the horizontal lithotomy position. In both groups, the operating table was kept level with the patient's back flat and the head elevated on a pillow. The legs were lifted simultaneously into stirrups by the nurse.

Five, 10, 15, 30, and 60 minutes after injection of spinal anesthetic, blood pressure, heart rate, and anesthesia sensory level were recorded. When surgery was completed in less than 1 hour, the 60-minute data were recorded in the recovery room with the patient supine. Otherwise, the 60-minute values were determined in the operating room in the surgical position. Sensory level was defined as the level at which a 25-gauge needle moved cephalad along both midclavicular lines could be felt. If the level on the two sides differed, the values were averaged. Landmarks were T12 inguinal canal, T10 umbilicus, T8 costal margin, T6 xiphoid, and T4 nipple.

After the initial bolus, the rate of infusion of IV fluids was kept to a minimum unless hypotension occurred. This was defined as systolic blood pressure below 100 or 33% below the preoperative value at the time of admission to the hospital. Hypotension was

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Received from the Department of Anesthesiology, Hackensack Medical Center, Hackensack, New Jersey. Accepted for publication April 26, 1988.

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Table 1. Comparison of Patients*

	Group A: wait ($n = 23$)	Group B: no wait ($n = 26$)
Age (yr)	69.6 ± 8.9	70.2 ± 7.3
Height (cm)	174.3 ± 5.6	171.6 ± 7.0
Weight (kg)	81.5 ± 11.7	79.5 ± 11.0
ASA class	2.2 ± 0.7	2.3 ± 0.7
Total fluid (cc)	791.5 ± 262.4	957.3 ± 480.4
Midazolam (mg IV)	1.3 ± 1.7	1.4 ± 1.7

*Values are means ± SD.

treated with additional IV fluid and 5-mg doses of IV ephedrine. Midazolam was given intravenously 10 minutes after induction of spinal anesthesia if sedation was necessary. Oxygen (4 L/min) via nasal cannula was administered after spinal injection until the patient left the operating room. On arrival in the recovery room, blood pressure and heart rate were recorded.

After all patients were studied, results were tabulated and analyzed using Student's *t*-test with $n1 + n2 - 2$ degrees of freedom and $P \leq 0.025$ being taken to indicate a statistically significant difference.

Results

One patient was eliminated from the study because spinal anesthesia failed. Table 1 shows that the 23 patients in group A and 26 patients in group B were similar in age, height, weight, and ASA classification.

Both groups received similar total volumes of fluid intraoperatively. One patient in each group was given packed red blood cell transfusion during surgery. Three patients in each group developed hypotension, which responded to IV ephedrine and fluid. The average dose of IV midazolam sedation was not statistically different in the two groups of patients.

Table 2 shows the average blood pressure, heart rate, and thoracic anesthesia sensory levels at various times in both groups. There was no statistically significant difference between these means for the two groups.

Discussion

Kitahara et al. (1) demonstrated that because of the lumbar lordosis of the spinal canal, hyperbaric anesthetic solutions injected into the lumbar subarachnoid space spread in cephalad and caudad directions. The extent of spread to the thoracic region depends on the inclination of the lumbar area.

Levin et al. (2) studied the effect of baricity on spinal tetracaine anesthesia for genitourinary surgery in the lithotomy position. After receiving the spinal anesthetic in the sitting position, all patients were placed supine for 5 minutes and then in the horizontal lithotomy position for surgery. Duration, latency, and level of sensory blockade, and incidence of bradycardia and hypotension were recorded. There was no statistical difference in these parameters between patients receiving hyperbaric versus isobaric tetracaine solutions. The effect of lithotomy compared to the supine position on anesthetic course was not studied.

Smith (3) studied patients given hyperbaric tetracaine spinal anesthesia in the lateral decubitus position before inguinal herniorrhaphy or TURP. One group of patients had their legs and thighs extended before turning to the supine position, while another group had their thighs flexed upon the abdomen during and after turning for 2 to 4 minutes. The flexed group had a maximum level of anesthesia approximately two dermatomes lower. It was believed that reduction in lumbar lordosis by flexion of the thighs had limited the cephalad spread of the hyperbaric anesthetic. Although the maximum anesthetic level varied, the average systolic and diastolic blood pressures showed no significant difference between groups. A difference in blood pressure may have been masked by the prophylactic IM injection of 50 mg ephedrine given to all patients at varying intervals before administration of the spinal anesthetic.

In our study and in clinical practice, when patients are placed in lithotomy position for TURP, the thighs are not flexed completely against the abdomen but kept at approximately right angles to the abdomen. In addition, in our study the spinal injection was performed in the sitting position and the table was kept horizontal, while in Smith's study the injection was performed in lateral decubitus position and the table was tilted with the patient's head up or down in several cases. These aspects of study design could explain why there was no difference in anesthesia sensory level observed in our patients placed immediately in horizontal lithotomy position compared to patients first kept supine for 10 minutes after receiving spinal hyperbaric tetracaine.

Recently Logan and Drummond (4) reevaluated Smith's findings using a blind assessment method, limiting hip flexion to 90°, and maintaining the operating table horizontal. They concluded that hip flexion does not significantly alter the level of anesthetic sensory blockade or cardiovascular effect.

One benefit of early leg raising would be if it provides an autotransfusion by preventing pooling of blood in the vasodilated lower extremities as the

Table 2. Blood Pressure, Heart Rate, and Thoracic Sensory Level with Time*

	Systolic blood pressure		Diastolic blood pressure		Heart rate		Thoracic sensory level	
Group	A†	B‡	A	B	A	B	A	B
Preop	138.3 ± 13.6	132.3 ± 18.3	81.8 ± 8.0	79.1 ± 9.7	75.4 ± 9.7	75.2 ± 8.9	—	—
0 min.	154.0 ± 21.3	160.3 ± 19.7	84.0 ± 12.1	86.7 ± 9.4	74.4 ± 19.1	76.0 ± 12.9	—	—
5 min.	144.5 ± 21.4	143.8 ± 24.5	75.3 ± 12.9	77.8 ± 12.5	75.0 ± 18.0	80.5 ± 14.1	10.8 ± 1.3	10.5 ± 1.2
10 min.	137.7 ± 22.1	136.9 ± 23.0	70.2 ± 13.8	73.7 ± 12.8	76.0 ± 19.2	78.0 ± 13.9	9.4 ± 1.5	9.3 ± 1.1
15 min.	131.1 ± 21.7	129.3 ± 21.3	70.6 ± 11.4	71.5 ± 10.8	74.7 ± 20.2	74.0 ± 12.2	8.7 ± 1.5	8.0 ± 1.3
30 min.	127.3 ± 18.1	125.5 ± 19.0	68.5 ± 12.7	70.9 ± 10.6	68.4 ± 16.0	70.1 ± 11.9	7.9 ± 1.7	7.7 ± 1.4
60 min.	130.7 ± 24.5	125.7 ± 18.7	71.8 ± 16.6	74.6 ± 12.4	65.3 ± 13.5	69.0 ± 12.8	8.1 ± 1.8	7.6 ± 1.7
Postop	127.8 ± 25.5	126.3 ± 17.1	75.3 ± 16.1	77.4 ± 12.0	66.2 ± 11.3	68.9 ± 11.4	—	—

*Values are means ± SD.
†Group A: wait supine 10 minutes.
‡Group B: immediately horizontal lithotomy.

spinal anesthetic causes sympathetic blockade. The similarity of anesthesia level, blood pressure, and heart rate in both groups suggests that early leg raising did not alter the anesthetic course. The fact that blood pressure was also similar on arrival in the recovery room, implies that lowering the legs at the end of the case did not uncover a need for more fluid therapy in either group.

Because there appears to be no difference in anesthesia level or hemodynamic changes achieved by postponing patient positioning for TURP for as long as 10 minutes, we recommend positioning the patient immediately in horizontal lithotomy after spinal anesthesia is given. This does not alter the anesthesia sensory level when the operating table is maintained horizontal. After positioning the patient, the surgeon takes several minutes to drape the patient and prepare for surgery, allowing time for the anesthesia to take effect. Because the first surgical step is insertion of the cystoscope, which requires only a low level of anesthesia, we found that surgery could start quickly after the patient was positioned. In our 26 patients who were first kept supine for 10 minutes waiting for the anesthesia to become at least partially fixed, 260 minutes of operating room time could have been saved if they had been placed in surgical position immediately. Considering the frequency of TURP under spinal anesthesia and the cost of operating room and anesthesia times, it is important to know that it is not necessary to wait to place the patient in horizontal lithotomy position after the spinal anesthesia is administered.

In conclusion, we studied 50 patients scheduled for elective TURP under hyperbaric tetracaine spinal anesthesia. There was no statistically significant difference in anesthesia sensory level, blood pressure, or heart rate in patients placed immediately in horizontal lithotomy position compared to patients first kept supine for 10 minutes after receiving the spinal anesthetic. Placing the patient immediately in the horizontal lithotomy position saves operating room time and does not alter the anesthetic course of the patient.

We thank the anesthesia, urology, and nursing staff at Hackensack Medical Center, especially Mark Schlesinger, MD, and Donna Delia, RN, BSN, for assistance. We are indebted to Professor Anthony Adrignola for expert statistical analysis.

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Effect of Stellate Ganglion Block with Fentanyl on Postherpetic Neuralgia with a Sympathetic Component

Perry G. Fine, MD, and Michael A. Ashburn, MD

Key Words: INFECTIONS—herpes zoster. ANESTHETIC TECHNIQUES, REGIONAL—stellate block. SYMPATHETIC NERVOUS SYSTEM, STELLATE GANGLION—block. ANALGESICS, FENTANYL—stellate block.

The sympathetic nervous system has been repeatedly implicated as an important factor contributing to various pain syndromes ever since the 19th century when Mitchell first defined causalgia (1,2). Patients with postherpetic neuralgia (PHN) often present with burning pain and allodynia similar to that seen with sympathetically mediated pain syndromes. Some authors have found sympathetic blocks to be useful in treating patients with PHN with these symptoms (3,4). On the basis of reports of the presence of opioid receptors in sympathetic autonomic ganglia in many species, including tissue(s) from the human stellate ganglion (5–8), we recently used the synthetic opioid fentanyl in a standard stellate ganglion block in a patient with PHN whose pain symptoms were refractory to other conventional therapeutic interventions.

Case Report

A 61-year-old man was referred to our pain clinic because of pain in the left upper chest, axillary area, and medial distribution of the left arm for 1 year after a herpes zoster infection. The pain was described as constant, burning, severe, and rated as usually 9–10 on a 0 to 10 analog scale. Any movement of the left arm induced sharp jabbing pains radiating down the left arm that were rated as a 10. He had tried numerous palliative treatments, including psychological pain management, occupational and physical therapy, and a variety of medications, including tricyclic antidepressants, antiepileptics, nonsteroidal anti-inflammatory drugs, and many different narcotics, phenothiazines, and steroids. None of these had an effect on the severity of his symptoms. He stated he had become completely inactive due to his pain and was getting, at most, 2 to 3 hours of continuous sleep at night.

This married man had taken an early medical retirement from his employment as an engineer because of this unrelenting pain. His medical history was also remarkable for moderately severe chronic obstructive airways disease. When initially seen, his daily medications included theophylline, albuterol, metaproterenol, cromolyn sodium, prednisone, carbamazapine, and Triavil (perphenazine and amitriptyline).

Examination revealed an aesthenic man with the stigmata of chronic obstructive pulmonary disease and steroid usage who guarded his left side and held his left arm motionless. He had characteristic postzoster scarring in a T1–T4 dermatomal distribution on the left with coincident hyperalgesia, patchy hypesthesia, dysesthesia, and hyperpathia, especially along the axillary fold areas and down the medial aspect of the arm. Testing for motor function and range of motion was not possible because of pain and voluntary movement of the left arm at the shoulder was restricted to a few degrees in all planes. The affected arm and hand were cool and clammy, the left hand being 6°C cooler than the right (30 v 36°C).

A diagnosis of postherpetic neuralgia with associated sympathetically based pain was made. Initial therapy consisted of tapering daily doses of carbamazapine, discontinuing the Triavil, and very slowly increasing nocturnal doses of amitriptyline, along with efforts to mobilize the affected arm.

After several weeks the patient was tolerating 100 mg amitriptyline and was enjoying frequent full and restful nights of sleep, but still had the same level of activity-induced pain during the day. The spontaneous burning and jabbing pains were only slightly reduced.

A series of left stellate ganglion blocks using local anesthetics was initiated with substantial but only transient pain relief lasting a few hours. In view of the intractable nature of this patient's pain and few

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Received from the Department of Anesthesiology, University of Utah Health Sciences Center, Salt Lake City, Utah. Accepted for publication April 27, 1988.

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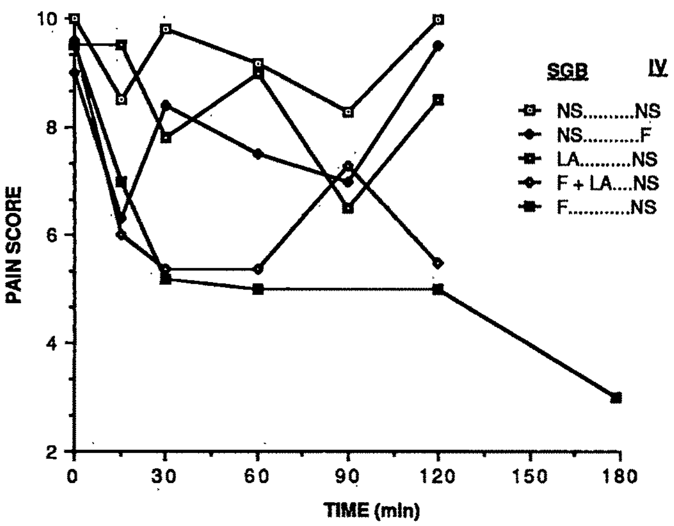

Figure 1. Pain as a function of time after concurrent stellate ganglion block (SGB) and intravenous (IV) injections of combinations of normal saline (NS), fentanyl (F) and/or lidocaine (LA).

useful therapeutic options available (neurosurgical options are controversial at best, and this patient was an exceedingly poor surgical candidate), with informed consent we undertook the trial injection of an opioid onto the stellate ganglion.

On separate days, the patient received an injection, using the standard approach to the stellate ganglion, of either lidocaine 100 mg, fentanyl 100 μg, lidocaine 80 mg plus fentanyl 100 μg, or normal saline, all in volumes totalling 10 ml and given in randomized order. Simultaneously, an IV injection of normal saline or fentanyl 100 μg was given in combinations as shown in Figures 1 and 2. The intravenous injection of fentanyl allowed differentiation of the systemic effects of fentanyl and localized effects caused by the drug applied as a stellate ganglion block. All injected substances were identical in appearance and prepared by an uninvolved physician. The patient, the physician injecting the agents, and the postinjection evaluator were unaware of what was injected. All injections were carried out by the same anesthesiologist using the anterior, paratrachial, C–6 level approach.

Digital temperature, pain scores (linear visual analog scale), physical examination for sensory changes, and subjective descriptions were recorded. Follow-up information on duration and quality of pain relief, if any, for each pair of injections, was obtained. The order of stellate injections turned out to be: 1) lidocaine plus fentanyl (IV placebo), 2) lidocaine only (IV placebo), 3) placebo (IV fentanyl), 4) fentanyl only (IV placebo), and 5) placebo (IV placebo).

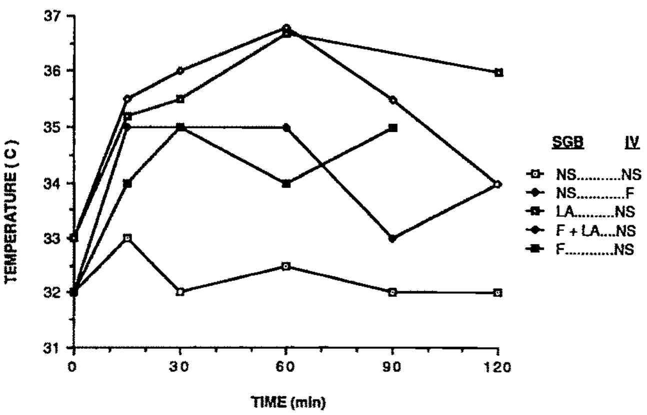

Figure 2. Digital temperature as a function of time after concurrent stellate ganglion block (SGB) and intravenous (IV) injection of combinations of normal saline (NS), fentanyl (F) and/or lidocaine (LA).

Results

As demonstrated in Figure 1, the stellate blocks with fentanyl or local anesthetic with fentanyl provided the most profound and enduring pain relief. The effect of the block with local anesthetic alone was consistent with previous unblinded block results in this man. Digital temperature changed inversely with pain scores, demonstrating a sympatholytic effect, though in the trial of intravenous fentanyl this was probably of central origin rather than a local effect on the ganglion (Fig. 2). Based on these results, we proceeded with three more lidocaine-fentanyl stellate blocks over the course of a week. The patient obtained significant pain relief for about 2 weeks and, with adjunctive physical therapy, full range of motion of the left arm returned.

A schedule of similar blocks was instituted every 2 weeks, resulting in continued pain relief, full use of the arm, and disappearance of allodynia and dysesthesia over the next 3 months. At that time, without informing the patient, fentanyl was excluded from the block. On routine follow-up 2 weeks later, the patient spontaneously volunteered that this had been the worst period he had experienced since instituting this therapy. His pain had returned after 2 days and he could not attribute this to anything specific. Based on this, we have continued the fentanyl blocks on an every-other-week basis with continued pain relief and functioning for 6 months.

Discussion

Laboratory studies have demonstrated the presence of opioid peptides and receptors in autonomic ganglia and that opioids can modulate sympathetic activity through actions on these neuronal receptors (5–9). The mechanisms involved in these actions have not been fully elucidated, nor has the normative role of this endogenous system been clearly defined.

In our patient, fentanyl given intravenously provided brief reduction in pain while the same dose injected as a stellate block provided more marked and prolonged pain relief. This suggests that the response experienced by this subject was due to a specific activity at the site of injection, namely the cervicothoracic sympathetic chain, rather than via a systemic effect of fentanyl.

It is realized that one cannot draw reliable inferences from observations made in a single case, even with a blinded and randomized design. Nonetheless, this particular patient's response was, and continues to be, remarkable when compared to prior attempts at palliative treatment. This case brings to the fore not only basic physiologic theories and observations concerning the role of the sympathetic nervous system in modulating pain and the presence of endogenous opioids in sympathetic ganglion (5–11), but also possible new clinical methods for the management of certain types of pain. Our clinic referral pattern does not, however, include adequate numbers of patients with similar problems to investigate the potential value of our observation in a large number of patients. It is hoped that presentation of this case report will stimulate thought to clarify the potential utility of opioids to modulate ganglionic activity as well as to benefit patients who suffer from pain syndromes that may be intractable to present therapies.

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Letters to the Editor

Do Dopaminergic Drugs Really Prevent Opiate-Induced Rigidity?

To the Editor:

We were quite interested to see the recent letter (1) suggesting that amantadine, a drug that appears to stimulate release and inhibit reuptake of dopamine in the basal ganglia, may prevent fentanyl-induced muscle rigidity. Based on their clinical experience, Silbert and Vacanti raise some provocative questions. Given the complexity of the neuropharmacology of opiate rigidity and the limited animal data supporting a dopaminergic component to this form of muscle rigidity, it is unfortunate that the authors were only able to present a single case report.

While we can not scientifically state that amantadine pretreatment does or does not attenuate opiate-induced rigidity, we have reason to be skeptical of the findings in a single patient. After having quantified rigidity using electromyography in over 100 patients (2,3) and several thousand rats, it is clear to us that there is tremendous individual variation in the expression of opiate rigidity. In addition, subjective assessment of rigidity does not always correlate well with either electromyographic or mechanographic measures. Last, Silbert and Vacanti's patient received 10 mg of diazepam 1 hour before induction of anesthesia. Our human data (see Fig. 1) demonstrate that diazepam is relatively effective at attenuating alfentanil-induced rigidity. It is therefore possible that the failure of Drs. Silbert and Vacanti's patient to exhibit rigidity could have been due to the diazepam premedication and not to the amantadine. The "pill rolling tremor" they describe is intriguing, although it is not uncommon for patients made rigid with alfentanil to exhibit coarse jerking arm and hand movements.

It should be stressed that the neurochemical basis of opiate-induced rigidity is probably very different from that of phenothiazine-induced rigidity (4). The paper cited by Silbert and Vacanti (5) describes the role of a dopamine-specific neostriatal subregion in *haloperidol* (not opiate) rigidity. Several recent studies (6,7) failed to demonstrate any role for the neostriatum in opiate-induced muscle rigidity. Interestingly, the recent work of Jerussi et al. (8) suggests that neither dopamine agonists or antagonists are particularly effective at antagonizing fentanyl rigidity in rats. In fact, their study provides much stronger evidence for α-2 adrenergic involvement in opiate rigidity. Work in our laboratory has substantiated the hypothesis of others that brainstem sites containing serotonergic and GABAergic pathways play a crucial role in the expression of opiate rigidity (9,10).

We would also like to respond to the speculations regarding possible opiate-Parkinsonian interrelationships. MPTP, a "designer" meperidine derivative, produces Parkinsonism by destroying the dopaminergic cell bodies in the substantia nigra (11). The drug does *not* have any opioid activity (12). Despite the widespread use of high-dose opiates in anesthesia and chronic pain for many years, there have never been any reports (or even suggestions) of opiate-induced Parkinsonian symptoms.

It is clear that the neurochemistry of opiate rigidity is complicated and multiple brain regions and transmitter pathways probably mediate this undesirable effect of high-dose opiates. The selection of effective pretreatment regimens to prevent opiate rigidity must be based on a sound scientific foundation, begun in the laboratory and substantiated with controlled clinical trials. A single patient does not a study make.

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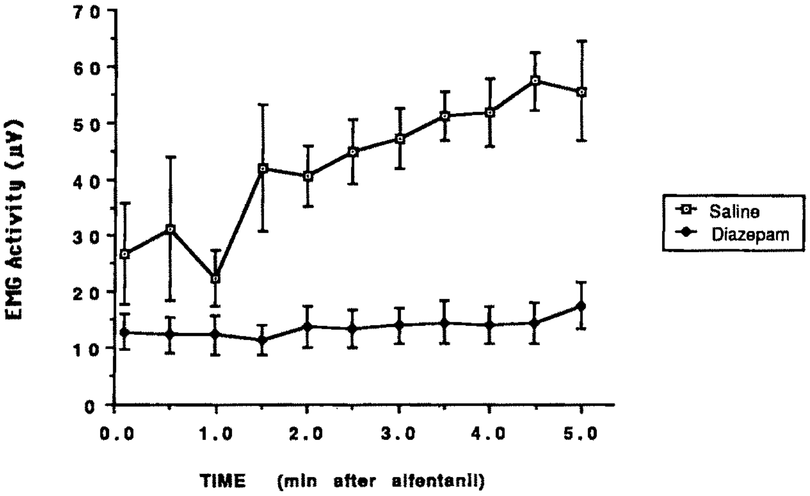

Figure 1. Effects of diazepam pretreatment on alfentanil-induced muscle rigidity. The figure presents the degree (mean ± SEM) of alfentanil-induced muscle rigidity over time in patients pretreated with either IV saline (n = 9) or diazepam (5 mg, n = 5) 5 minutes before induction of anesthesia with alfentanil. At time zero, each patient was given alfentanil (175 µg/kg IV) and then electromyographic activity was recorded from the intercostal muscles over the next 5 minutes. Diazepam pretreatment produced a significant ($P < 0.05$ by ANOVA) attenuation of rigidity compared with saline after the first 1.5 minutes. Unfortunately for the clinician wishing to prevent opiate rigidity, the addition of diazepam to this large induction dose of alfentanil may result in detrimental hemodynamic changes.

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In Response:

After careful review of the letter by Weinger et al., we feel that several of their comments were based on a misunderstanding of the intent of our letter. We would like to annotate their points of dispute.

First, we clearly stated that we realized "this single case was inadequate to prove" anything and, "it may be some time before we can complete a formal study." That is precisely why we submitted it as an interesting observation in a letter rather than as a clinical report or a scientific article. Second, we are quite familiar with their published work in humans. As a matter of fact, their publication concerning the effect of various pretreatment regimens (1), which may have incorrectly concluded that thiopental does not affect narcotic induced muscle rigidity, influenced us to inappropriately use thiopental in this patient. We have since demonstrated that thiopental can indeed influence narcotic-induced muscle rigidity (2). We do agree that diazepam may also have affected the degree of rigidity in our patient. Third, though the work of Jerussi et al. (3) may suggest that neither dopamine agonists or antagonists are effective at antagonizing fentanyl rigidity in rats, Wand e t al. (4) clearly demonstrated in rats that dopamine inhibits morphine-induced muscle rigidity. We agree that seratonergic and GABAergic pathways may play a crucial role, and that the neurochemistry of opiate rigidity is complicated, involving multiple brain regions and transmitter pathways.

Results of a study depend not only on the model used, but also the dose of a drug as well as its route of administration. Indeed, Turski et al. (5) in 1982 demonstrated that morphine itself, when injected into the pars compacta of the substantia nigra, antagonized the rigidity observed after systemic administration of morphine, whereas injection into the pars reticulata enhanced it.

I believe the reasons for sharing our interesting observations concerning amantidine are valid. Although amantidine may not be a specific treatment of the end organ involved in the mediation of opiate induced muscle rigidity, the pathways involved are intricate and the use of amantidine may attenuate the rigidity and be helpful in elucidating the mechanisms involved.

In summary, we do not believe that Dr. Weinger and his associates will disagree with the following conclusion, as stated in their own paper in 1986: "Although of completely different etiologies, the final common pathway of narcotic rigidity may be shared by some of the motor abnormalities seen in Parkinson's disease and extrapyramidal drug reactions" (6).

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Repeat Cesarean Section in a Patient with Previous Cortical Vein Thrombosis

To the Editor:

Younker et al. (1) reported on anesthetic problems associated with management of three patients with cortical vein thrombosis during pregnancy and delivery. We wish to report follow-up of Patient 3 at the time of a subsequent delivery.

The patient's previous delivery was accomplished as described by Younker et al. (1) by cesarean section because of severe pregnancy-induced hypertension and cephalopelvic disproportion. Her postoperative course was complicated by coagulopathy, generalized seizures, decreased mental status and hemiparesis. After CT scan revealed cortical vein thrombosis and diffuse edema, a ventriculostomy was performed. She remained hospitalized for 10 days and then made a complete neurologic recovery. She was discharged home on diphenylhydantoin and methyldopa.

At the time of the present admission (3.5 years later) she presented in early labor as a G2P1 at 40 weeks gestation. Blood pressures, neurologic examination, and laboratory data were all within normal limits. She was taking no medications. A repeat cesarean section was planned. Epidural anesthesia was chosen to allow close observation of mental status during surgery. In addition, postoperative analgesia using epidural narcotics could be provided without use of systemic medications that might obtund her sensorium or alter the neurologic examination. An epidural catheter was placed at the L3–4 interspace and a sensory level of T3 obtained using incremental doses of lidocaine 2% with epinephrine and 100 μg fentanyl. A female infant was delivered and found to have a true knot in the umbilical cord and Apgar scores of 5 and 9. Umbilical arterial *p*H was 7.22 and venous *p*H 7.31. The mother received 5 mg epidural morphine for postoperative pain relief and remained in the recovery room for 24 hours for repetitive neurologic examinations. She did well and was discharged from the hospital on the fifth postoperative day.

There is little information in the literature on follow-up of patients with cortical venous thrombosis or the anesthetic recommendations for later surgical procedures. Biback et al. (2) reported a delivery by cesarean section under spinal anesthesia in a patient with cerebral vein thrombosis in a previous pregnancy. However, the diagnosis of cerebral vein thrombosis was made on purely clinical grounds without CT or angiographic documentation, and the interval between deliveries was not specified. Srinivasan (3) reported a series of 129 women with cerebral venous thrombosis during pregnancy, five of whom became pregnant again within 18 months and delivered normally without recurrence of symptoms. No mention is made of anesthetic or surgical intervention. Lorincz and Moore (4) described six patients, two of whom had subsequent uncomplicated pregnancies at 2 and 3 years after their thrombosis occurred. One had spinal anesthesia for curettage and one had general anesthesia for forceps delivery without problems.

It would be helpful to know in patients such as the one on whom we now report whether the initially involved vessels have recanalized to reestablish flow. Imai et al. (5) reported a case of cerebral venous sinus thrombosis diagnosed by CT scan and radionuclide flow study that occurred at 20 weeks gestation. An angiogram performed 6 months later because of recurrent headaches confirmed patency of the superior sagittal sinus.

Although definite recommendations are difficult to make, it appears that there is a good prognosis for subsequent pregnancies in these women. Anesthetic management should be based on the patient's neurologic status and medical and obstetric conditions at the time of delivery.

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Direct Arterial Pressure Monitoring in Humans

To the Editor:

Dr. Brandt's recent interesting letter concerning the history of human oral intubation (1) suggests parallels in other advances in anesthetic practice. Approximately 40 years ago, Peterson et al. (2) continuously recorded brachial artery pressure using a flexible polyvinyl resin catheter. We believe this was the first time this method of recording arterial pressure was used in humans. Furthermore, the unique use of an ink-writing oscillograph permitted a continuous and permanent blood pressure recording of obvious relevance to anesthetic patient care (3).

Before the above, percutaneous direct measurement of arterial pressure during surgery became a possibility after development of the hollow metal needle in the mid-19th Century. The immediate problem was, however, trans-

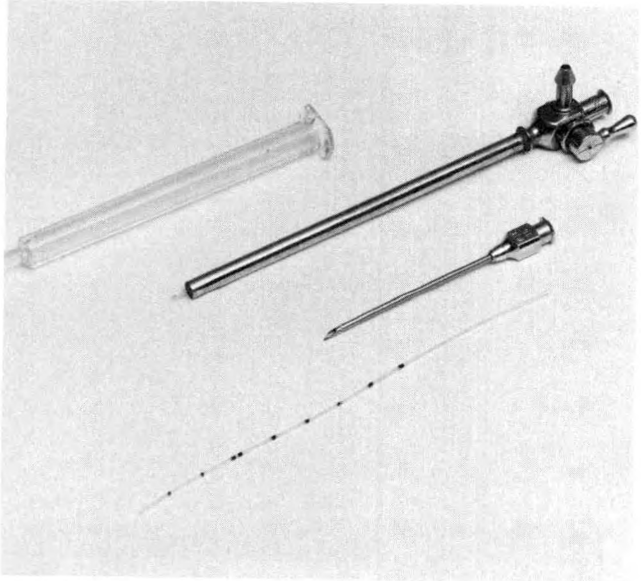

Figure 1. Device components from top to bottom: syringe, plunger, needle, and catheter.

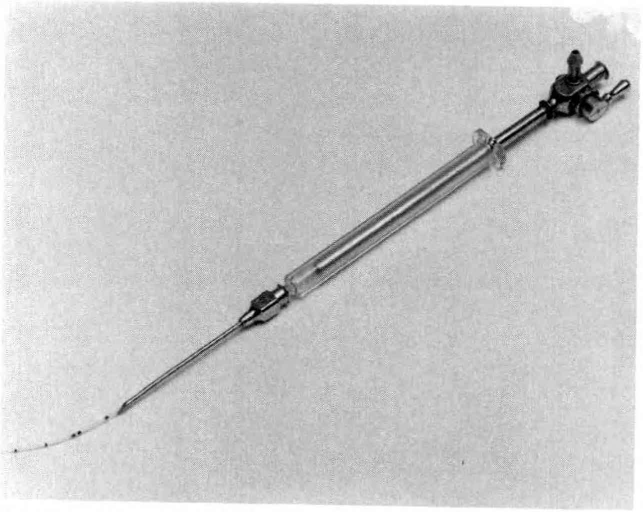

Figure 2. Assembled device.

ducing such arterial pressures. It was not until 1934 that Hamilton developed a brass shim membrane, giving an optical tracing of blood pressure using a needle cannula. Such a system was used in 1936 to measure brachial artery pressure in humans in the absence of surgery (4) and, in 1940, during surgical anesthesia (5). In 1943, Bruchthal and Warburg (6) presented similar brachial artery pressure data obtained using a capacitance manometer. Lambert and Wood (7) later also reported direct intravascular pressure monitoring using the radial artery during human centrifuge studies. Again, arterial access was by a direct needle stick with the pressure being transduced using a resistance wire strain gauge.

Finally, Peterson et al. (2) published a method for recording arterial blood pressure in humans using a technique that became the precursor of today's methods. One of the innovations Peterson et al. introduced was the substitution of a plastic catheter for a rigid metal needle with, thus, the potential for greater limb mobility, easier fixation, and a reduced incidence of secondary arterial puncture. The catheter was placed over a small nipple on the end of a hollow steel plunger ground to fit a 1-ml syringe filled with sterile saline. Using a custom thin-walled 22-gauge needle on the end of the 1-ml syringe, the catheter was withdrawn through the needle by withdrawing the plunger. The artery was then punctured using the 22-gauge needle and the plunger of the syringe depressed with injection of the catheter into the artery. The needle was then withdrawn from the artery, leaving the intra-arterial catheter in place. The components and the assembled device are shown in Figures 1 and 2. In the Figures, a regular 16-gauge needle and a piece of marked epidural catheter tubing are shown for the purposes of clarity. After arterial insertion, pressure changes were recorded by connecting the catheter to a capacitance manometer. A further innovation was the use of an ink-writing oscillograph, allowing for continuous and immediate observation of blood pressure changes.

Over the last 40 years, the methods of Peterson et al. (2) have been refined by the use of over-the-needle Teflon catheters, disposable manometers and progressively more portable and flexible recording equipment.

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Partial Lung Ventilation Test for Differentiating Esophageal and Laryngeal Intubation

To the Editor:

Oxygen desaturation shown on the monitor is often a late sign of esophageal intubation. To affirm laryngeal intubation, the routine use of simple auscultation, observing the "fogging" of the tube, assessing the expiratory volume, etc., are unreliable (1); even CO_2 detection has been questioned (2). Vigilance and the use of several methods together would improve the chance of a correct diagnosis. The following simple test has been used to confirm laryngeal intubation.

When a patient has been intubated in the usual manner but one is not sure if it is endotracheal or esophageal, the tube is pushed gently all the way downward toward the bronchus as far as it can go without trauma. IPPB is then initiated while five points auscultation is carried out at both apices, the sides of the chest bilaterally and the epigastrium. The test is positive for laryngeal intubation if there are breath sounds on one side or part of the lungs with absence of breath sounds in the other (often the left). The test is negative in esophageal intubation, the breath sounds then being either bilaterally equal in intensity or equally diminished or absent on both sides of the chest. Epigastric auscultation and other methods used to differentiate laryngeal from esophageal intubation would also be useful in assisting the diagnosis. The test is based on the intentional but transient creation of endobronchial intubation and ventilation. If the tube is too small in size to seal off one of the bronchi (gently inflated cuff might be desired), or if the tube is too short to reach the bronchus, then the test might be inconclusive. Naturally, the unequal ventilation in the lungs pathologic in origin might negate the reliability of test.

I have used this technique the past 12 years whenever an esophageal intubation was suspected. In the several hundreds of occasions when this test was performed, less than ten times has the test been inconclusive; correct diagnosis was eventually confirmed in all cases by using combinations of other methods.

This partial lung ventilation test is not foolproof. It is another simple means to differentiate laryngeal from esophageal intubation. It has been quite helpful to me in the past years.

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Socioeconomic Status and Arterial pH

To the Editor:

The article by Bland et al. (1) contains the statement, "Mothers in both groups had evidence of mild metabolic acidemia, presumably due both to 12 hours of fasting and the patients' low socioeconomic status." I was heretofore totally unaware of the relation between socioeconomic status and arterial pH. Several important questions arise in this regard.

1) Is it possible to treat an acid-base disorder without knowing the social history of a patient?
2) Should a nomogram be developed to assist physicians in relating family income to the solution of acid-base problems?
3) Should the Henderson-Hasselbalch equation be rewritten to include variables for income or education or world stock prices or the price of gold in London?
4) Can bicarbonate therapy help alleviate poverty?

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In Response:

Dr. Marschall's comments concerning the effects of social status on maternal acid base parameters, while entertaining and amusing, cannot be left unchallenged.

Crawford has commented in the past on the issue of poverty and maternal biochemical status (1,2). My own experience, gleaned over a period of 16 years anesthetizing members of a poor community in the province of Natal, South Africa, concurs with the views he expressed then (3–14). Black Zulu Mothers generally manifest a greater degree of metabolic acidemia when presenting for elective cesarean section than that usually reported in the literature. These latter studies have usually involved women who are not poor.

If Dr. Marschall's experience among underprivileged women has been different, perhaps she should share with us the benefit of her findings by publishing them!

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Migration of an Arterial Catheter

To the Editor:

The migration of an epidural catheter into the subarachnoid space or into a vessel is now a well-described entity. A case involving the possible migration of an intra-arterial catheter into a vein was recently encountered that will be of interest to readers.

A 64-year-old man was being managed in our intensive care unit after repair of a ruptured abdominal aortic aneurysm. Because difficulties were encountered in weaning off controlled ventilation, he had a tracheostomy performed on day 14 in the unit.

On day 21 in the unit, his arterial blood gases at 0920 hours. (Fio_2 0.49) were: pH 7.42, Pco_2 4.90, kPa (36.79 mm Hg), Po_2 13.2, kPa (99.13 mm Hg), and O_2 saturation 97.6%. At this stage, the patient was on SIMV (synchronized intermittent mandatory ventilation) of five breaths/min, PEEP (positive end-expiratory pressure) of 5 cm H_2O, and a pressure support of 15 cm H_2O. The latter is a mode whereby when the ventilator senses a patient breath and the ventilator can assist the inspiration using a preset positive pressure. This mode has been found to be extremely useful in situations where patients become increasingly exhausted during the weaning period.

At 1340 hours (after the patient had been sitting out of bed for an hour) blood gases were: pH 7.31, Pco_2 6.84, kPa (51.36 mm Hg), Po_2 9.0, kPa (67.59 mm Hg), and O_2 saturation 89.4%, on the same ventilator settings. One hour later the arterial gases were: pH 7.33, Pco_2 6.71, kPa (50.39 mm Hg), Po_2 6.40, kPa (48.06 mm Hg), and O_2 saturation 79.4%. Clinically the patient looked as he did in the morning, with no obvious deterioration in any of his other vital signs. Blood gases again measured after half an hour were: pH 7.43, Pco_2 5.22, kPa (39.20 mm Hg), Po_2 4.90, kPa (36.79 mm Hg), and O_2 saturation 71.60%.

A chest x-ray at this stage was normal, with no evidence of a pneumothorax. The samples of arterial blood we were obtaining were from the right radial artery. It was thus decided to take a sample from the left radial artery, soon after the last sample was obtained from the right side. The results were: pH 7.53, Pco_2 3.90, kPa (29.28 mm Hg), Po_2 11.70, kPa (87.86 mm Hg), and O_2 saturation 97.80%. The site of arterial cannulation on the right arm was then examined after removal of all dressings. The catheter had been in situ for 48 hours. It is important to note that the right radial artery had been previously cannulated on initial admission and the catheter left in situ for 5 days. The catheter used on both occasions was a 20-gauge (standard wire gauge) Teflon catheter 51 mm long. The catheter on both occasions was inserted right up to the hub.

On examination of the site, the catheter was not obviously kinked at the hub, and there was no swelling. Aspiration of blood through the catheter was very easy. When the intra-flow device was disconnected from the catheter, there was no backflow of blood. As we were not using the arterial line to monitor blood pressure, arterial waveforms had not been monitored.

The most likely explanation for the aberrant results is that the catheter migrated into a nearby vein while the patient was sitting out of bed. The main arteries of the upper limb are accompanied by the pairs of deep venae comitantes (1) which can be of considerable size. The cephalic vein, at its origin, lies in the superficial fascia just posterior to the radial styloid and then runs on the anterior aspect of the forearm. This vein can occasionally run superficial to the radial artery at the site of the wrist (1,2).

In the case presented here, due either to (a) the type of catheter used or (b) weakening of the arterial wall due to previous cannulation, the catheter could have migrated either into the cephalic vein near its origin, or into the venae comitantes that accompany the radial artery. Fortunately the patient did well, and examination of the right radial artery site 2 weeks later revealed no swelling or clinical evidence of an A-V fistula.

This case once again stresses that we should not forget to look at patients; clinical assessment is just as, if not more, important than relying solely on numbers to guide us.

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A Simple Method of Measuring ETco_2 During MAC and Major Regional Anesthesia

To the Editor:

Monitoring of ETco_2 with mass spectrometric methods is rapidly becoming commonplace during the administration of general anesthesia. Many anesthesiologists are, how-

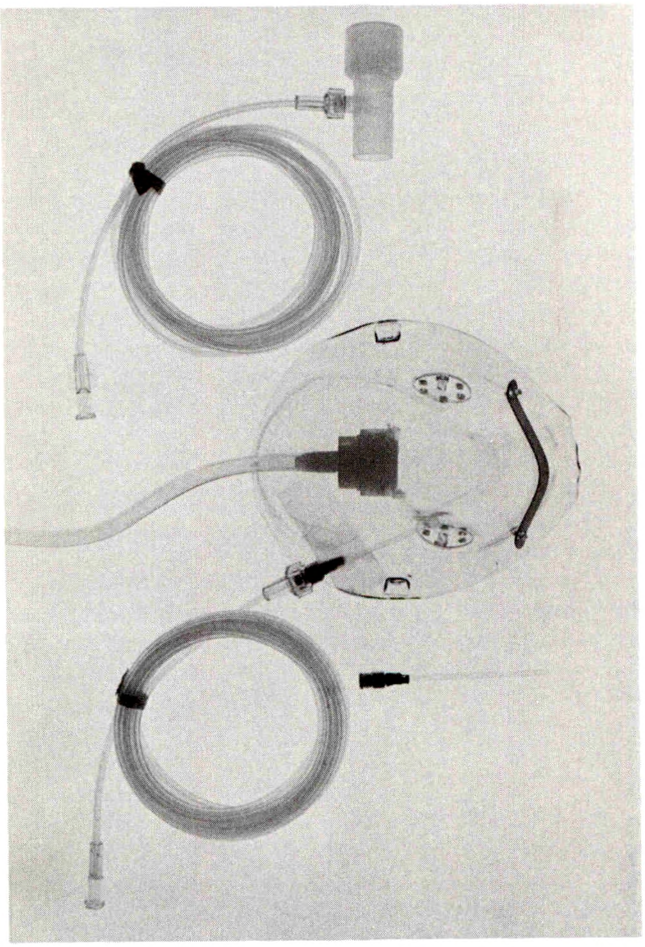

Figure 1. Standard capnograph tubing at top with modified tubing shown below.

ever, dissuaded from using this monitor during major regional anesthesia or monitored anesthesia care (MAC), because of the absence of an endotracheal tube or a tight fitting face mask with, therefore, the potential entrainment of room air into the tubing used for delivery of gas to the capnograph. Monitoring of respiratory parameters in the patient during regional anesthesia is, however, no less important than under general anesthesia and often will aid in early detection of potentially catastrophic events (1). A method of monitoring both ETco$_2$ and respiratory rate that is usable in these circumstances is as follows. Remove from a standard capnograph or mass spectrometer tubing the T-piece fitting for an endotracheal tube connection. Replace the T-fitting with a #14-gauge plastic IV cannula with the needle removed. This can be placed through the side holes of a loosely fitting face mask used for the insufflation of oxygen (Fig. 1). The proximal end of the capnograph tubing is hooked to the sampling port of the capnograph in the usual manner. For greatest stability of the catheter, it can be taped to the side of the plastic oxygen mask with a short piece of plastic tape.

If an ETco$_2$ waveform is displayed on a screen, relative changes in tidal volume as well as in respiratory rate and ETco$_2$ can be obtained. Because the mask is not tight-fitting and room air will often be entrained through the holes in the mask, the reading for ETco$_2$ will not be as accurate as with a more closed system (e.g., endotracheal tube or standard anesthesia mask). However, if the plastic IV catheter is trimmed so that its tip is at the nares, accuracy will be improved. The digital measurement of respiratory rate on the capnograph will be highly accurate. This technique has been used successfully during 20 opthalmologic procedures under MAC and 25 cases of high-level epidural anesthesia for cesarean section. In almost all cases this technique yielded highly satisfactory results.

This technique should be especially useful during management of patients having local anesthesia during, for example, MAC opthalmic surgery when the patient's face and upper chest are often covered with drapes and CO$_2$ retention is more likely. Assessment of relative tidal volume and respiratory rate will also be aided by this technique.

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Mechanism of Propofol Bradycardia

To the Editor:

In their recent report, Cullen et al. (1) demonstrated the role of baroreflex control of heart rate during propofol anaesthesia: resetting of the set point allows slower heart rates despite decreased arterial pressures. However, to our knowledge, no studies have been done of direct actions of propofol on sinus node or atrioventricular conduction. Recently, two mongrel dogs were anesthetized with thiopental (10 mg/kg) and pancuronium (0.2 mg/kg) for insertion of intracardiac electrode catheters (transvenously, from femoral vein to the heart: one bipolar in the right atria, one quadripolar in the right ventricle, allowing the detection of the His bundle potential). R–R, P–R, QRS, A–H, and H–V intervals were then recorded before and each minute for 10 minutes during and following successive propofol injections of 2.5, 5, and 10 mg/kg. Dog 2 also received, before propofol injection, atropine (0.1 mg/kg) and propanolol (0.2 mg/kg) to induce pharmacologic autonomic denervation of the heart. The results show dose-dependent decreases in heart rate and a decrease in arterial blood pressure in both dogs (Table 1), without change in QRS or conduction intervals. A decrease of the sensitivity of the baroreflex control of heart rate may explain slower heart rates despite decreased arterial pressures (1) in dog 1, but the increase in RR intervals in the autonomically denervated dog under propofol anesthesia suggests there may also be a direct effect of propofol on sinus activity comparable to that seen with anion antagonists like alinidine (2).

Table 1. Summary of Data

	Before propofol injection		5 min after 10 mg/kg propofol	
	BP (mm Hg)	RR (ms)	BP (mm Hg)	RR (ms)
Dog 1	141	275	117	400
Dog 2	133	370	77	550

Dog 1: autonomically intact; Dog 2: autonomically denervated with atropine and propranolol. BP, mean arterial blood pressure; RR, R-R interval.

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Bradycardia After Alfentanil–Succinylcholine

To the Editor:

Although several studies (1,2) have emphasized the cardiovascular stability associated with alfentanil when employed for induction of anesthesia, we recently observed bradycardia and sinus arrest in a patient given a relatively small bolus dose. A 51-year-old, 67-kg woman, healthy except for a moderate smoking history, mild arthritis, and lobular carcinoma of the breast, previously treated with bilateral simple mastectomies and prosthetic implants, was scheduled for elective staged plastic repair of her right breast. She had no significant cardiac history and took no prescription medications.

After being premedicated with midazolam 1 mg IV and while receiving oxygen by mask, she was given *d*-tubocurarine 3 mg IV and alfentanil 1500 μg (22 μg/kg) IV. She was then anesthetized with thiopental 150 mg IV and given succinylcholine 100 mg IV in preparation for tracheal intubation. Immediately before laryngoscopy, while systemic blood pressure was 104/58 mm Hg, ECG-monitored heart rate slowed precipitously from sinus rhythm at 68 beats/min, and a 10-second asystolic period ensued. Pulselessness was confirmed by physical examination and loss of the pulse oximeter signal. Tracheal intubation and ventilation with 100% O_2 were quickly accomplished, upon which sinus rhythm immediately resumed at 48 beats/min without pharmacologic therapy, and blood pressure returned to 100/50 mm Hg. The remainder of the anesthetic was uneventful.

Vagally-mediated bradycardia is a common side effect of fentanyl-derived analgesics (3), especially when given in large bolus doses. It is conceivable that succinylcholine-induced ganglionic stimulation interacts with narcotic-enhanced vagal tone to lower the analgesic dose required to produce heart rate slowing. Specifically, Maryniak and Bishop (4) have reported the occurrence of sinus arrest after combined alfentanil (30 μg/kg)–succinylcholine administration, as have Sherman et al. (5) after sufentanil (0.8 μg/kg)–succinylcholine.

In the case reported herein, sympathetic stimulation from tracheal intubation presumably overcame the heightened vagal tone and restored sinus initiation of cardiac contraction. Administration of atropine would have been logical and was imminent, if sinus arrest had continued. We conclude that in bolus doses, alfentanil, like sufentanil, can cause dangerous heart rate slowing when given in combination with succinylcholine. Pretreatment with atropine or pancuronium would likely prevent these effects.

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Book Reviews

Malignant Hyperthermia

Beverly A. Britt, ed. Boston, Martinus Nijhoff, 1987, 420 pp. $48.95.

Dr. Britt has edited this book with the stated goals of recommending ways to detect malignant hyperthermia (MH) susceptibility before surgery, to provide anesthesia safely to MH-susceptible people who require elective operations, to diagnose an acute MH crisis early during anesthesia or other stressful situations, and to treat MH reactions effectively. To this end, the editor has brought together many experts on various aspects of MH and has produced an informative, readable text with extensive, up-to-date references.

The review of current popular theories of the etiology and pathophysiology of MH (Chapter 2) is particularly lucid. Sarcoplasmic reticulum function is reviewed in detail (Chapter 3) and there are very clear discussions of the consequences of increased phospholipase A_2 activity (Chapter 4) and calcium-induced calcium release (Chapter 5). Chapter 7 is a basic, well written review of the complex genetic aspects of MH and suggests a unified workable genetic explanation. Chapters 9-12 address all muscle tests presently used to diagnose MH around the world. The problems of nonuniformity in different laboratories is tackled as well as the issue of false-negative and false-positive tests. Much of the book concentrates on the laboratory research aspects of MH; therefore, the book should be read by anyone who is doing basic research in MH, associated with a muscle biopsy laboratory, or wants a detailed review of the pathogeneses of MH. Clinicians will find discussions on counseling the MH-susceptible patient (Chapter 13), updates on dantrolene (Chapter 14) and detection (Chapter 1), and treatment (Chapter 16) of an MH episode. Thus, the book answers many practical question for the clinician and discusses in detail the clinical aspects of treating MH-susceptible patients.

Controversial problems that face the clinician that are not mentioned or need more discussion include: If anesthesiologists are going to avoid triggering agents in patients who have negative biopsies, which is, in effect, treating these patients the same as positive-biopsy patients, then why get a biopsy at all? What are the implications for the family (lifestyle, insurance, armed services, stress jobs) when a patient is labeled as MH-susceptible (with or without a muscle biopsy)? In light of new data on masseter muscle rigidity and jaw tightness after succinycholine, is it safe to continue anesthesia in the patient having elective surgery who has this response? Is lidocaine with epinephrine safe for dental use? How long should an MH-susceptible patient who has done well be kept in the recovery room? Is MH-susceptibility a contraindication to outpatient anesthesia? Also, authors of various chapters are not in complete agreement about some issues, such as the need for and dose of dantrolene for prophylaxis, as well as the reliability of the muscle biopsy.

To summarize, this book is an up-to-date review of MH and should be read by anyone interested in current theories of MH and the pitfalls of diagnostic tests for MH. The book answers many clinical questions and is a significant step forward in the clinical care of MH-susceptible patients.

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Cardiovascular Problems in Pediatric Critical Care

Swedlow DB and Raphaely RC, eds. New York: Churchill Livingstone, 1986, 311 pp, $42.00.

This is a very good book, the intent of which is to provide a solid understanding of the basics of cardiovascular physiology and to facilitate their application to the care of the critically ill infant or child. It succeeds in doing so. It is not, nor is it intended to be, a textbook of congenital heart disease.

The first of nine chapters is an excellent treatment of cardiovascular physiology with special attention paid to developmental aspects and provides a solid foundation for the remainder of the book. The effects of preload, afterload, and contractility on isolated muscle and intact heart are nicely discussed, followed by sections covering the integration of pump function with that of the child's autonomic nervous system and vascular tree. The chapter is extensively referenced and may alone be worth the price of the book.

Chapters discussing the noninvasive and invasive assessment of the failing circulation follow. Although their content is somewhat uneven, good coverage of echocardiographic and radionucleide imaging of the heart is included, and practical approach to vascular catheterization, transduction of waveforms, and the pitfalls of these techniques, is presented.

A chapter on anesthetic management of children undergoing cardiac surgery follows. The discussion is nicely

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done, stressing the planning of the anesthetic to achieve desired effects on the individual determinants of cardiac output. The chapter seems somewhat out of character with the rest of the book because of its focus on children with congenital heart disease. Its inclusion may be justified, however, because of the intensivist's need to care for these children in the general pediatric critical care unit.

The manipulation of preload and afterload to augment the failing circulating are discussed in two chapters, the former in greater detail than the latter. The chapter on myocardial contractility competes with chapter one for being the best chapter in the text. There is a nice discussion of myocardial energetics, coupled with a review of the factors influencing energetics, oxygen supply and, thus, contractility. The practical application of these principles to clinical care is presented in a clear, straightforward manner.

The final chapters of the book discuss cardiac rhythm, dysrhythmias, and cardiopulmonary resuscitation. Although the various dysrhythmias are adequately covered, the discussion of rhythm generation and its aberrancies is not in great depth. The CPR chapter presents a good overview of factors distinguishing pediatric from adult resuscitation, and properly stresses the importance of restoration of coronary perfusion pressure. However, the discussion of drug administration is not completely in line with the most recent recommendations of the American Heart Association.

In summary, this book is an excellent complement to the other volumes in its series, and will be an important addition to the library of any physician caring for critically ill children. It is complete enough to serve as a useful reference text yet provides explicit clinical guidance to the resident or fellow. Its emphasis on the cardiovascular problems encountered in the care of the previously normal child is unique and refreshing.

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Neonatal Anesthesia

D. Ryan Cook, Joseph H. Marcy, eds. Pasedena:
Appleton Davies, 1988: 262 pp, $52.50.

Anesthesiologists have long resisted sanctioned subspecialization. However, the body of information which must be mastered for successful consultation in anesthesia to our surgical and medical colleagues who *are* subspecialized continues to grow and is beyond the ability of any individual to master. Even within the subspecialty of pediatric anesthesia, dramatic advances during the last two decades in the understanding of the physiology, pathophysiology, and care of the critically ill and premature neonate now demands special expertise to care for this subpopulation. Available general anesthesiology texts cover this body of knowledge superficially while current texts devoted to the anesthesia care of children do only an incomplete job. This text, a product of the staff at the Children's Hospital of Pittsburgh, nicely fills this void.

There are 12 chapters in this monograph; the first 4 are devoted to the unique physiology that characterizes the newborn, including: "Cardiovascular Physiology of the Fetus and Newborn," "Respiratory Physiology," "Persistent Pulmonary Hypertension of the Newborn," and "Thermoregulation of the Newborn." All of these chapters are well written, well referenced and are state of the art in their content. Schieber's chapter on cardiovascular physiology is particularly good, and almost worth the price of the book by itself. That chapter and the excellent chapter on persistent pulmonary hypertension provide the reader with a thorough overview of the most unique physiologic consideration for an anesthesiologist caring for the newborn, the transition of the circulation from the fetal to the extrauterine circuit.

The chapters on "Parenteral Fluid Therapy," "Pediatric Anesthetic Pharmacology," and "Pediatric Breathing Circuits" provide the ground work for the specifics of intraoperative management in the following chapters. All anesthesiologists would especially benefit from the concise, straightforward treatment of breathing circuits provided.

"Basic Neonatal Anesthesia and Monitoring" and "Common Surgical Conditions of the Newborn" are, the editors admit, "how we do it," but the advocated approach is well reasoned and well referenced. The succinct but complete information on the prevalent surgical diseases of the newborn exemplifies why this text is successful and other efforts have failed.

"Neonatal Resuscitation" and "Respiratory Care" are requisite discussions of the related critical care medicine topics as applied to this special population. They are easy to read and complete, and the references provide a useful source for further investigation of these topics. The last chapter, "Medical Ethics and the Neonatal Anesthesiologist," is unusual and provides a brief important introduction to a topic that deserves more of our attention.

This is an important new addition to the library of anesthesiology texts. Any practitioner who routinely cares for infants and all post-residency trainees in pediatric anesthesia should be familiar with this book.

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Medical Management of the Surgical Patient, Second edition

Michael F. Lubin, H. Kenneth Walker, Robert B. Smith, eds., Boston: Butterworths, 1988, 692 pp.

A large textbook that proceeds to a second edition in 5 years, which is what this work has done, must be considered a success. It is surprising perhaps because the book is about surgical patients and was written as an aid to medical consultants, but it is very pleasing that the spirit of cooperation and interdependence between specialists that the editors envisaged has apparently been popular. The three editors and 59 contributing authors (mostly from the Emory University School of Medicine in Atlanta) have produced a work that is worthy of the best traditions of medical practice described first in the time of Hippocrates and repeated in their introduction: "Nor among physicians, do those who treat by diet envy those who employ surgery, but they call each other into consultation and commend one another."

The text is in two main parts: preoperative and postoperative care of the surgical patient, and surgical procedures and their complications. Part one is in 16 sections with between 1 and 6 chapters each, while part two is composed of 10 sections each with between 5 and 18 chapters. The content is really quite comprehensive and should, of course, be a major source of reference to all clinicians who come into contact with a surgical patient. As each chapter is authoritative and well referenced, the work fulfills this role quite well. Figures and tables are relatively few, but the text itself is divided into headings at frequent intervals.

There is only one section comprising three chapters that is specifically entitled "Anesthesia and the Surgical Patient," although many other sections are of interest to anesthesiologists. The section includes chapters entitled "Methods and Goals of Anesthesia," "Effects of Anesthetic Agents and Techniques on Body Systems," and "The Risk of Anesthesia and Surgery." These chapters are a little disappointing in that they are quite short and would not stand alone in a textbook of anesthesiology. However, that is probably editorial design, and the main aim of the book is to give the nonexpert some knowledge of the various aspects of care of surgical patients.

With the warning that this large and comprehensive text is a little superficial in its coverage of at least some subjects, one would wish to recommend it as valuable reference and the type of book which one might want to have available in the postoperative recovery ward, high-dependency units, and in surgical wards. It would be good if surgeons read it, but I think that is unlikely. Anesthesiologists will find it interesting at times, but the major market will be physicians who are called frequently to consultations on surgical wards.

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Positive Airway Pressure Therapy: PPV and PEEP

Barry Shapiro, Roy D. Cane, eds. Philadelphia: WB Saunders, 1987, 205 pp, $20.00.

To many clinicians, mechanical ventilation and various forms of oxygen and pressure therapy for respiratory failure have been an uninterpretable serving of alphabet soup—CPPV, CPPB, CPAP, etc. The editors of this text have made a concerted effort to standardize terminology from 18 different contributors. This process of standardization begins with the book's preface and carries through all 205 pages and 14 chapters.

In the past 30 years of mechanical ventilation, there has been a trend from control mode ventilation (CMV), which worked well in patients with neuromuscular respiratory failure, to progressive patient participation in the ventilation process during respiratory failure. The trend began with assist/control mode ventilation (A/CMV) and progressed through intermittent mandatory ventilation (IMV) to new techniques. This text, in various chapters, traces this historic change and looks at the equipment components which were necessary for patient participation. M. Christine Stock's chapter on standard modes of ventilation begins the process by looking at patient participation and work of breathing, and John Downs' chapter on new techniques of ventilation concludes the story by looking at new modes of patient participation such as pressure support ventilation (PSV).

The editors, in constructing the text, chose to take a physiologic approach to the discussion of airway pressure therapy rather than a purely engineering or mechanical approach. Chapters on cardiopulmonary effects by Christine Chomka and acute lung injury by Barry Shapiro illustrate the physiologic approach. The text is clearly not an exhaustive discussion of the pathophysiology of various forms of respiratory failure, but rather a physiologic approach to an essentially mechanical topic.

I would conclude that the authors achieved their goal of standardizing and simplifying the topic of airway pressure support. The book should be a basic part of the anesthesiology resident's and critical care fellow's introduction to the diagnosis and management of respiratory failure.

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Introduction to Anesthesia, The Principles of Safe Practice, 7th Edition

R. D. Dripps, J. E. Eckenhoff, L. D. Vandam.
Philadelphia: WB Saunders, 1988, 512 pp, $29.00.

One book, above all others, has continued to hold primacy in the United States for the last three decades as an introductory text for students and residents in anesthesiology. First published for internal use at the University of Pennsylvania in 1949 and 1953, the present edition constitutes the seventh to be made available to the general public since 1957. It is the third volume to be published after Dr. Dripps' death in 1973. The price of the first edition was

$4.75, which is approximately one-sixth of the current price. Given the great inflation in textbook prices that have occurred in the intervening years, the present price is not inappropriate.

The two senior authors have continued in the current version a long-standing practice of enlisting contributors; 5 new collaborators join 16 veterans in this edition. All are professional descendants of the original three authors, having been educated by and/or having been members of their respective departments at Harvard University, Northwestern University, and the University of Pennsylvania. However as Drs. Eckenhoff and Vandam comment in the preface, " . . . the overall conception, stylistic embellishment, and responsibility are still those of the two of us." It is noteworthy that many of the line drawings by Dr. Vandam that appeared in the first edition continue to lend clarity in the seventh.

The general organization of the current volume is essentially unchanged from the sixth edition, with sections on "The Broad Realm of Anesthesiology," "Essential Preanesthetic Considerations," "Anesthesia and Operation," and "Ancillary Anesthesia Care." The 36 chapters average about 13 pages and are ideal for the fledgling who needs to grasp the general principles of a narrowly defined subject rather than many of the more particular details. The tightly edited text with virtually no surplus verbiage (which has been a hallmark of previous versions) has been continued in this edition; despite the fact that ten percent of the text is written by new authors, their styles have been fully integrated with those of the continuing writers. Each chapter provides a short list of pertinent references; as an innovation, citations of historic interest have been set off from more current citations in several chapters. This small and welcome change facilitates the use of the references for directed reading. Each chapter has been updated without significant enlargement. In fact, the new edition has only 18 more pages than its predecessor. Given the advances that have occurred in the past 6 years, it is remarkable that it has been possible to limit the growth of this volume.

One new chapter on opioids has been added to the new edition. It is difficult to adequately encompass even the bare outline of the vast amount of new knowledge that has been discovered in recent years about the molecular and clinical pharmacology of this important class of drugs and the densely written text does not make easy reading. One wishes that it had been possible to enlarge this particular section to more completely treat this rapidly burgeoning area of interest. There is some duplication of material in this chapter and the one on pain therapy. It is noteworthy that the latter section has no consideration of acute pain management, especially postoperative pain, which is rapidly becoming more important as part of the practice of anesthesiology. One wishes that there had also been a treatment of new methods of parenteral opioid administration, particularly the use of patient-controlled analgesia.

The senior authors from the time of the first edition have chosen to present fundamental concepts and broad principles while leaving specific details of technique and dosage to other writers. For example, there was no consideration of specialized topics such as pain management, deliberate hypotension, and specific techniques of regional anesthesia in the early editions. Although these specific limitations no longer apply, this editorial policy has been continued in this edition. This has probably been wise, because it lends a certain timelessness to the book. However, there is such a paucity of detail that the beginning resident will need to supplement this volume with one of several excellent handbooks that are available as a source of specific details of technique and drug dosage.

As expected, the content and scope of this book has undergone considerable metamorphosis over the past three decades. There are a wide variety of topics which were treated in the early editions which are now passe. In a separate appendix, "Remembrance of Things Past," there is a listing of many topics, techniques, equipment, and anesthetic agents which are no longer of import to the specialty. These serve as a reminder to both established practitioners and trainees that despite the transitory nature of many aspects of our practice, one overarching challenge persists: to provide safe and humane care for our patients during a period of great personal stress.

The seventh edition is a highly useful introductory text by a cadre of renowned teachers. It should be in the library of every anesthesiology residency program and is highly recommended for medical students and residents in anesthesiology.

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Blood Transfusion in Clinical Medicine, 8th Edition

P. L. Mollison, C. P. Engelfreit, M. Contreras, eds.
Oxford, England: Blackwell, 1987, 1033 pp, $105.00.

Mollison's text is the classic reference on transfusion medicine, originally dating back to a first publication in 1961. The 8th edition, written by three authors, avoids duplication and has a high level of continuity throughout the text. The style is quite readable and clear, informative yet reasonably concise. Occasional historical notes embellish the text without detracting from its relevance. The book differs from other scientific texts in its relative paucity of diagrams and tables and its frequent reference to individual case reports. Some of this is inherent in the nature of transfusion medicine, a discipline in which it is difficult to initiate controlled, prospective studies in many important areas (such as transfusion reactions).

The text is remarkably current, with many subjects being referenced through 1987. Although only two pages long, the section on massive transfusion refers to the best current references on the subject and accurately surmises correct conclusions. The 13 pages in the chapter on infectious agents dealing with transfusion-associated HIV discuss this subject in detail. At least 300 pages of the text cover areas important to anesthesia such as red cell transfusion, components, hemolytic reactions, hemolytic disease in the newborn, and transfusion reactions. These areas make the book a handy reference to any anesthesiologist, even though much of the rest of the text stresses blood group serology.

Autotransfusion is an important topic in modern transfusion medicine and could have received much more stress in the text. Could this be a sign of the book's British heritage? Another distinguishing characteristic is the way this text lists no references at the end of each chapter, but collects all references into a 176-page section at the end of the book. Nevertheless, readers will find this text as worthwhile and up-to-date a reference as is available in the field of transfusion medicine.

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Anesthesia for Thoracic Procedures

Bryan E. Marshall, David E. Longnecker, H. Barrie Fairley, eds. Boston: Blackwell, 1987, 632 pp. $195.00.

The stated aim of this publication is to "provide the fundamental framework for the special requirements of anesthesia for thoracic procedures." Each chapter in itself is well organized and devoted to the titled topic with subsections labeled for easy reference. The early chapters on embryology, anatomy, pulmonary ventilation, blood flow and oxygenation, and pharmacology are well written. While there is a consistent attempt to provide as much information as possible, the clinical application of much of this information was often overlooked. More emphasis in these chapters on the changes occurring with thoracotomy (the primary focus of this text) would be welcomed.

The book progresses to chapters that seem more focused, such as a delightful description of the history of thoracic surgery, anesthesia, and the lung. The chapters concerning concomitant medical conditions, psychological preparation, the anesthetic plan, and control of infection during anesthesia, fail to focus on the specific relations between medical conditions, the anesthetic, and this particular type of surgery. On their own, these chapters could be a part of any edited edition textbook on anesthesia.

The section of the text dealing directly with specific procedures such as endoscopy, pulmonary surgery, tracheal resection, esophageal surgery, and mediastinal surgery are the substance of this book and cover the described topics in a complete and timely fashion. They can be recommended as an excellent source of information because they contain excellent, clinically applicable information that any anesthesiologist would welcome in a book dedicated to thoracic procedures. The closing chapters on the related topics of transplantation, postoperative care, and acute respiratory failure are well-thought out and well-written. A useful discussion of post-thoracotomy pain management, an area of major concern to the practicing anesthesiologist, included here is especially recommended.

In my opinion this text serves as a good reference source with valuable information that would be even stronger if applicability toward thoracic procedures were emphasized.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Anderton JM, Keen RI, Neave R. Positioning the Surgical Patient. Boston: Butterworths, 1988. 116 pp, $19.95.

Bond RF, Adams HR, Chandry JH, eds. Perspectives in Shock Research, Volume 264 of Progress in Clinical and Biological Research. New York: Alan R. Liss, 1988, 452 pp, $90.00.

Finucane BT, Santora AH. Principles of Airway Management. Philadelphia: FA Davis, 1988, 277 pp, $19.95.

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ISSN 0003-2999
Volume 67, Number 10, October 1988

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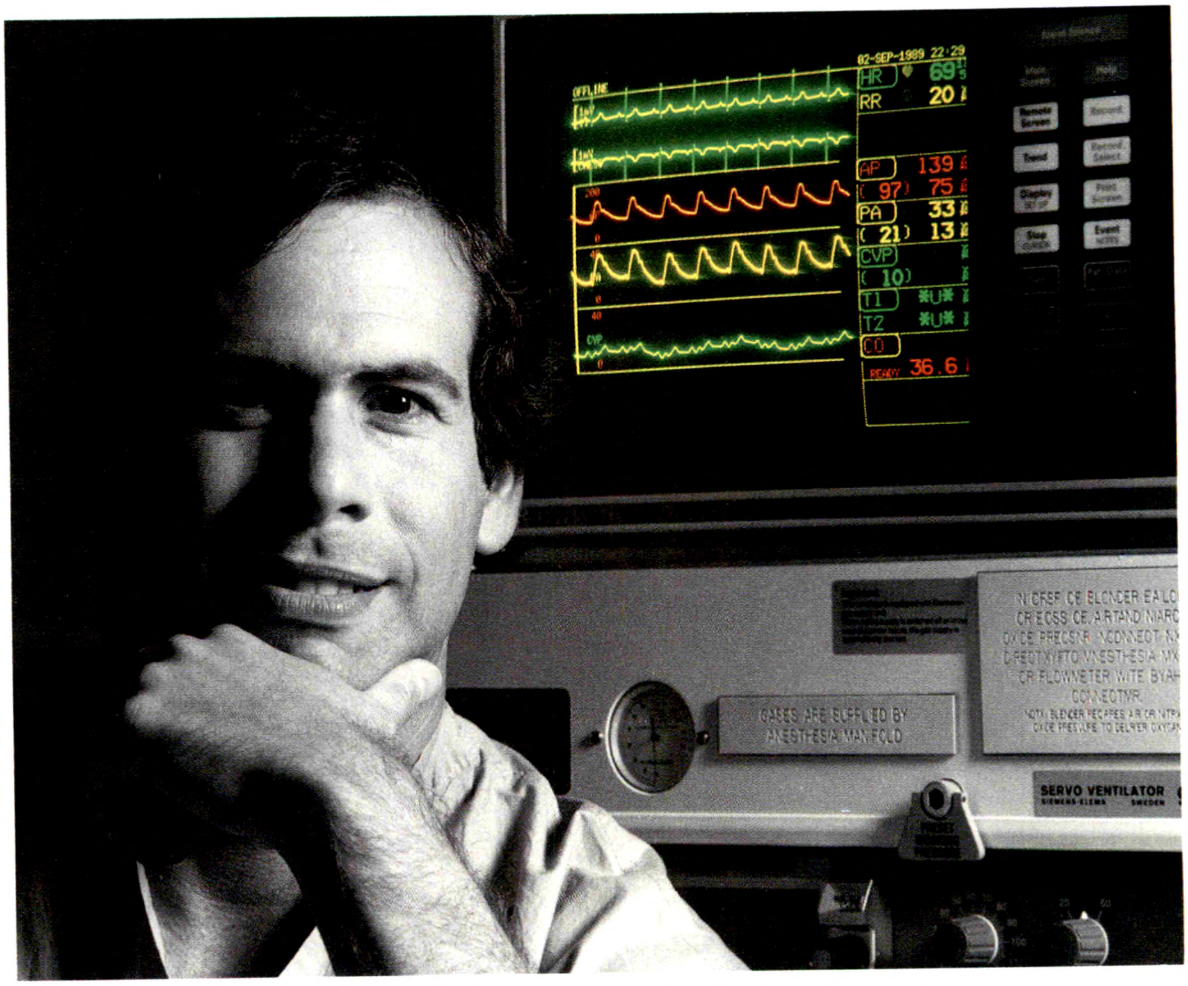

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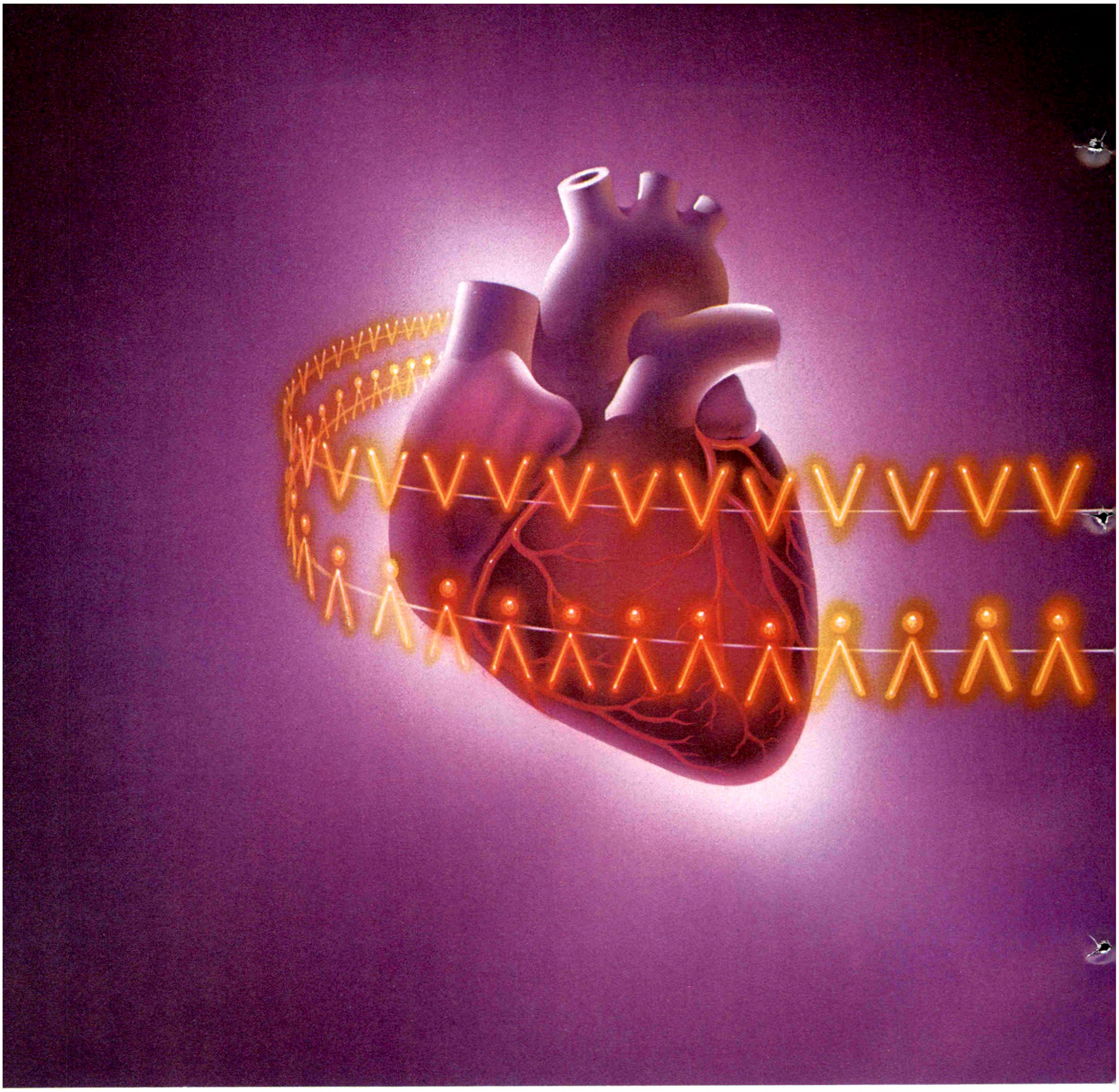

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Editorial

Survival Time during Hypoxia:

Effects of Nitrous Oxide, Thiopental, and Hypothermia

Alan A. Artru, MD

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, INTRAVENOUS—thiopental. HYPOTHERMIA—hypoxic survival. HYPOXIA—survival.

The "hypoxic mouse" model was first used by Arnfred and Secher in 1962 to determine whether barbiturate anesthesia prolonged survival time during hypoxia (1). Mice were placed in chambers where the $F_{I_{O_2}}$ was reduced to 0.05 and the time from onset of hypoxia to cessation of respiration was recorded. Since then the model has been used by numerous investigators to determine the efficacy of treatments that might enhance the tolerance to hypoxia, with the model being revised as more was learned about the variables that affect the results of its use (2–5).

In this issue of *Anesthesia and Analgesia,* Milde (6) presents results with this model in an article entitled "The Hypoxic Mouse Model for Screening Cerebral Protective Agents: A Re-examination." As this title implies, data on variables that affect the results with this model are presented. Specifically, Milde reports that the rectal temperature of untreated or thiopental-treated mice at ambient temperature of 35.5°C was 36.1°C and rectal temperature of untreated mice at 25°C was 36.5°C, whereas rectal temperature of thiopental-treated mice at 25°C was 30.4°C. The difference in rectal temperature between untreated and thiopental-treated mice at "room temperature" of 25°C is notable because mouse body temperature previously was reported to affect survival time in this model (3). However, the study focuses less on experimental variables and methodology, and more on the effect of nitrous oxide and/or thiopental on survival times.

Effects of Nitrous Oxide

One impetus for Milde's study appears to be a recent report by Hartung and Cottrell (7). These authors employed the hypoxic mouse model to examine the effects of nitrous oxide on thiopental-induced prolongation of survival time. Mice were tested one at a time in a single chamber. At ambient (unmeasured) temperature, survival time in thiopental-treated mice (13.9 ± 2.6 min, mean ± SEM) was significantly greater than survival time in untreated mice (5.2 ± 0.6 min). When 50% nitrous oxide was given along with thiopental, survival time was 4.8 ± 0.7 min; and when 50% nitrous oxide was given to untreated mice, survival time was 4.2 ± 0.3 min. The authors concluded that nitrous oxide reversed thiopental-induced prolongation of survival time.

Milde (6) objects that an important principle of the "hypoxic mouse" model was violated in Hartung and Cottrell's study, namely that multiple chambers should be used (one mouse per chamber) for each hypoxic challenge so that untreated and treated mice can be tested simultaneously. This precaution must be taken to insure that $F_{I_{O_2}}$ does not vary in the least between treated and untreated mice. Variations in $F_{I_{O_2}}$ as small as 0.005 significantly alter survival times with this model (2).

In the present study Milde (6) used three chambers (one mouse per chamber) for each hypoxic challenge. With no nitrous oxide present, untreated and thiopental-treated mice were tested simultaneously, and with 50% nitrous oxide present, untreated and thiopental-treated mice were tested simultaneously. This experimental design satisfies the above principle for use of this model when testing for an effect of thiopental on survival time—*but not when testing for an effect of nitrous oxide on survival time*—because untreated mice were not tested simultaneously with nitrous oxide-treated mice. Thus, Milde reproduces in part the same methodologic error for which Har-

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Received from the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington.

tung and Cottrell were criticized. With this in mind, the reader must choose how to interpret Milde's study (6) and that of Hartung and Cottrell (7).

One possible choice is to overlook the methodologic errors and accept that the four-group design (control, thiopental, nitrous oxide, nitrous oxide plus thiopental) tests for an effect of nitrous oxide on survival time. With this choice, Hartung and Cottrell's (7) results would be as valid as Milde's (6). The reader would accept the conclusion of Hartung and Cottrell (7) that nitrous oxide reverses thiopental-induced prolongation of survival time, and also accept the conclusion of Milde (6) that nitrous oxide has no effect on thiopental-induced prolongation of survival time. The reader could then conclude that the currently available data on the effects of nitrous oxide are inconclusive.

Another choice is to accept Milde's view (6) that her methodologic error is less severe than that of Hartung and Cottrell (7) and that her four-group design tests for an effect of nitrous oxide on survival time. In this case, Milde's data show that, compared to untreated controls at 25°C, survival time was unchanged with nitrous oxide, increased with thiopental, and increased to the same degree with nitrous oxide plus thiopental. Compared to untreated controls at 35.5°C, survival time was unchanged with thiopental and reduced with both nitrous oxide and nitrous oxide plus thiopental. The reader could conclude that nitrous oxide has no effect on survival time at 25°C but has a detrimental effect at 35.5°C.

Milde, on the other hand, concludes that nitrous oxide has no effect on survival time at 35.5°C, basing her conclusion on a comparison of the aforementioned survival time in nitrous oxide-treated mice at 35.5°C with survival time in two additional groups of untreated mice, one at 25°C and one at 35.5°C, that were not part of the original 35.5°C, four-group design. Because nitrous oxide did not shorten survival time when compared to these two additional untreated groups, Milde argues that her data fail to demonstrate any consistent effect of nitrous oxide. In making these latter comparisons, however, Milde has done the equivalent of what she criticizes Hartung and Cottrell for doing, namely, comparing results from treatment groups to a separately tested control group. If the reader accepts Milde's latter two comparisons, the reader overlooks all methodologic error and is actually making "choice one" as stated above.

A third choice is to not allow the methodologic error. In that case, Milde's four-group design does not test for an effect of nitrous oxide on survival time because the only treatments that were tested simultaneously were (i) control and thiopental and (ii) nitrous oxide and nitrous oxide plus thiopental. Thus the only valid conclusions relating to nitrous oxide that can be drawn from Milde's data are that at 25°C thiopental increases survival time both with and without nitrous oxide and at 35.5°C thiopental has no effect on survival time both with and without nitrous oxide. These results are consistent with the view that nitrous oxide does not alter survival time, but do not prove that view. To study the effect of nitrous oxide on survival time, mice receiving nitrous oxide (both with and without thiopental) should be tested simultaneously with mice not receiving nitrous oxide (both with and without thiopental).

Depending on what choices the reader makes in interpreting Milde's and Hartung and Cottrell's results, one can conclude that either (i) the results relating to the effects of nitrous oxide on survival time are inconclusive, (ii) nitrous oxide is detrimental at some temperatures and not at others, or (iii) an effect of nitrous oxide on survival time has not yet been properly measured.

Effects of Thiopental

As regards survival time in mice treated with thiopental, Milde states that "the prolonged survival attributed to thiopental in earlier studies is more likely due to hypothermia than to thiopental" (6). This statement is based on Milde's findings that at an ambient temperature of 35.5°C (which in a separate group of mice preserved body temperature at 36.1°C in thiopental-treated mice) thiopental did not improve survival time (6). However, at an ambient temperature of 25°C (where the body temperature of thiopental-treated mice fell to 30.4°C) survival time was increased with thiopental 100 mg/kg IP. Milde's (6) statement about thiopental, hypothermia, and survival time contains two issues that should be considered separately: namely, (i) Does thiopental prolong survival time during hypoxia? And, (ii) if thiopental does not account for the prolonged survival time in the mice given thiopental 100 mg/kg IP at 25°C, does hypothermia explain the prolonged survival time?

Milde's conclusion that thiopental does not improve survival time during hypoxia is supported by her findings that doses of thiopental ranging from 50 to 120 mg/kg IP produced no change in survival time in presumably normothermic mice (6). Many readers will probably be tempted to generalize this finding and to believe that it adds another bit of information to the already well-studied area commonly referred to as barbiturate-induced "cerebral protection." When studies with all barbiturates are lumped together, it is generally concluded that barbiturates provide "cerebral protection" during focal or global ischemia (8). In contrast, when only studies using thiopental are considered, people reviewing the studies who favor the "cerebral protection" idea would probably conclude that the results are inconsistent and may summarize them as follows: "During focal ischemia, Smith et al. (9) and Hicks et al. (10) reported 'cerebral protection' with thiopental, whereas Gelb et al. (11) reported no 'protection.' During global ischemia, Kofke et al. (12) reported 'protection,' whereas during global ischemia/anoxia Snyder et al. (13) reported no 'protection.' During hypoxia Michenfelder and Theye (14) reported 'protection,' whereas in the present study Milde (6) reports no 'protection.' " However, when considering the above findings one must remember that the popular term "cerebral protection" is a nonspecific one, and that what was actually measured in the above studies included one or two of the following: neurological status, histopathology, brain blood flow, brain glucose uptake, survival, and time-to-brain electrical silence. Milde confines her conclusions about thiopental to survival time and does not contend that survival time in this model is synonymous with or even related to "cerebral protection."

The second issue in Milde's statement about the effects of thiopental is that prolonged survival time in hypothermic, thiopental-treated mice is more likely due to hypothermia than to thiopental. This conclusion is based on Milde's findings that untreated mice at 25°C or 35.5°C and thiopental-treated mice at 35.5°C were all normothermic and survived hypoxia for 4 to 5 minutes, while thiopental-treated mice at 25°C became hypothermic (rectal temperature of 30.4°C) and survived for 11.8 minutes (6). The conclusion that prolonged survival time resulted from hypothermia would be more convincing if Milde had also demonstrated prolonged survival time in untreated mice with rectal temperatures of 30.4°C. However, Milde did not examine untreated mice at rectal temperature of 30.4°C. Instead, Milde cites two previous studies that examined the effect of hypothermia on survival time with this model. In one study (3) survival time of 2.9 minutes in chlorpromazine-treated mice at 37°C increased to 13.6 minutes when rectal temperature was reduced to 29°C. In the other study (16) survival time of 6.3 minutes in physostigmine-treated mice at 37°C increased to 8 minutes when intraperitoneal temperature was reduced to 35°C.

While these citations are consistent with hypothermia-induced increase of survival time during hypoxia, they do not prove that hypothermia would prolong survival time in untreated mice. However, such information is available in a study not cited by Milde. Using the same "hypoxic mouse" model as Milde, it was reported (16) that at an intraperitoneal temperature of 29°C mice survived hypoxia for 15.8 minutes, at 32°C mice survived for 11.2 minutes, at 35°C mice survived for 6.5 minutes, and at 37°C mice survived for 4.2 minutes. Control survival times were consistent with those reported by Milde and the results at 29 and 32°C indicate that hypothermia does prolong survival time in untreated mice. Considered in light of these results, Milde's statement that prolonged survival during hypoxia in hypothermic, thiopental-treated mice is more likely due to hypothermia than thiopental becomes more convincing. As noted above, care should be taken not to misrepresent Milde's statement on survival time by concluding that hypothermia and not thiopental "protects the brain" during hypoxia. In the "hypoxic mouse" model, survival time almost certainly is determined by the effects of treatments on many organ systems, not just the brain.

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The Hypoxic Mouse Model for Screening Cerebral Protective Agents: A Re-Examination

Leslie Newberg Milde, MD

MILDE LN. The hypoxic mouse model for screening cerebral protective agents: a re-examination. Anesth Analg 1988;67:917–22.

The hypoxic mouse model, in which mice are subjected to an atmosphere of 5% O_2 in nitrogen, has been used to screen anesthetics for possible cerebral protection by measuring their ability to prolong survival in mice exposed to hypoxia. Although prolonged survival time in this model is primarily due to a decreased cerebral metabolic rate produced by a specific anesthetic, results can also be influenced by body temperature, dose of anesthetic, and ventilatory or circulatory depression produced by the anesthetic. Using the hypoxic mouse model, the effects of thiopental in conjunction with changes in ambient temperature, changes in thiopental dose, and the presence or absence of nitrous oxide (N_2O) were examined. Survival times were measured in eight groups of animals, either untreated animals or animals pretreated with 100 mg/kg thiopental intraperitoneally; exposed to hypoxia in the presence or absence of N_2O; at ambient temperatures of either 25°C or 35.5°C. Survival times of seven additional groups of mice, either untreated or treated with doses of 50, 60, 70, 80, 90 or 120 mg/kg thiopental intraperitoneally, exposed to hypoxia in an ambient temperature of 35.5°C were measured to determine a dose–response curve. At an ambient temperature of 35.5°C in which the rectal temperature of both untreated and thiopental-treated animals was maintained near 36°C, thiopental-treated animals did not survive any longer than the untreated animals. Mean survival time was 4.32 ± 0.44 minutes in the thiopental-treated animals and 5.04 ± 0.28 (± SE) in the untreated animals. Exposure to N_2O shortened survival times of both groups by approximately 20%. Varying the dose of thiopental had no effect on survival times. However, when similar groups were studied in an ambient temperature of 25°C, survival time in thiopental-treated animals (11.84 ± 2.21 minutes) was significantly longer than in untreated animals (4.82 ± 0.37 minutes) studied simultaneously. At 25°C, exposure to N_2O before and during hypoxia did not alter the survival times; i.e., thiopental-treated animals survived significantly longer (11.59 ± 1.52 minutes) than untreated animals (6.14 ± 1.10 minutes) in 50% N_2O, 5% O_2. At an ambient temperature of 25°C untreated mice maintained rectal temperatures at 36.5°C, whereas those given thiopental had a significant decrease in body temperature to 30.4°C during the study period. In conclusion, the interference with thermoregulation produced by thiopental results in hypothermia if measures are not taken to maintain body temperature, and this hypothermia accounts for the prolonged survival observed with thiopental. Furthermore, N_2O has little effect on survival in the hypoxic mouse model.

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, INTRAVENOUS—thiopental, pentobarbital. BRAIN—hypoxia, protection. HYPOTHERMIA. HYPOXIA—cerebral.

Since 1962 when it was first described (1), the hypoxic mouse model has been used to screen anesthetics for their ability to increase tolerance of the brain to hypoxia. In this model, mice are subjected to an atmosphere of 5% O_2 in nitrogen and their survival time is recorded. Prolonged survival times have been reported for mice anesthetized with thiopental, halothane, cyclopropane (2), mephobarbital (3), pentobarbital (4), midazolam (5), and isoflurane (6). It has recently been reported that nitrous oxide (N_2O) abolishes the prolonged survival time provided by thiopental in this model (7).

Although the hypoxic mouse model is based on a simple concept, the results are influenced by several variables. Survival times are presumed to be due primarily to the cerebral metabolic rate produced by the anesthetic: the lower the cerebral metabolic rate, the longer the survival. Small differences in inspired oxygen concentrations markedly affect the survival time of barbiturate-treated animals, but have little effect on untreated animals (8). Similarly, differences in the time between the intraperitoneal injection of

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Received from the Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota. Accepted for publication April 28, 1988.

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Table 1. Mean Survival Times of Untreated and Thiopental-Treated Mice Exposed to Hypoxia ± N_2O at Two Different Ambient Temperatures

Group	*n*	Drug	Atmosphere	Ambient temperature	Survival time (mean ± SE) (minutes)
1	20	—	21% O_2/N_2 — 5% O_2/N_2	25°C	4.82 ± 0.37
2	18	Thiopental	21% O_2/N_2 — 5% O_2/N_2	25°C	11.84 ± 2.21*
3	18	—	21% O_2/50% N_2O/N_2 — 5 % O_2/50% N_2O/N_2	25°C	6.14 ± 1.10
4	18	Thiopental	21% O_2/50% N_2O/N_2—5 % O_2/50% N_2O/N_2	25°C	11.59 ± 1.52*
5	31	—	21% O_2/N_2 — 5% O_2/N_2	35.5°C	5.04 ± 0.28
6	22	Thiopental	21% O_2/N_2 — 5% O_2/N_2	35.5°C	4.32 ± 0.44
7	36	—	21% O_2/50% N_2O/N_2 — 5 % O_2/50% N_2O/N_2	35.5°C	4.05 ± 0.22†
8	16	Thiopental	21% O_2/50% N_2O/N_2 — 5 % O_2/50% N_2O/N_2	35.5°C	3.44 ± 0.22†

*Significantly different from untreated group ($P < 0.05$ with Bonferroni correction).
†Significantly different from group 5 ($P < 0.05$ with Bonferroni correction).

barbiturate and the onset of hypoxia affect survival time (8), as does dose of barbiturate (4). Increased arterial carbon dioxide tension ($Paco_2$) can prolong survival (2). The barbiturates can depress ventilation, causing an increase in $Paco_2$, which increases cerebral blood flow and prolongs survival (2). Ambient temperature may affect body temperature if thermoregulation is affected by the anesthetic. A decrease in body temperature of only 2°C significantly prolongs survival time (8). If not strictly controlled, the ambient temperature can be changed rapidly by the high gas flow rates (6–20 L/min) passing through the chamber in which the animals are exposed to hypoxia. Experiments of untreated and treated animals must be done simultaneously to control for small changes in ambient temperature and inspired oxygen concentration. In the study that reported that N_2O abolished cerebral protection by thiopental (7), ambient temperature was not controlled nor were untreated and thiopental-treated animals studied simultaneously.

The purpose of the present study was to study the effects on survival time of thiopental in conjunction with changes in ambient temperature, varying concentrations of thiopental, and the presence or absence of N_2O.

Materials and Methods

This study was approved by the Animal Care and Use Committee and the Research Committee of the Mayo Clinic. Two hundred forty-three adult male Swiss white mice, weighing 26–43 g, with free access to food pellets and water, were studied. One hundred seventy-nine mice were divided into eight groups (as shown in Table 1) to study the effects of thiopental, N_2O, and ambient temperature on survival time. Groups 1–4 were studied in an ambient temperature of 25°C; groups 5–8 were studied in an ambient temperature of 35.5°C. Groups 1 and 5 were untreated and breathed 21% O_2 in N_2 for 15 minutes before being switched to the hypoxic mixture. Groups 2 and 6 were treated with thiopental (100 mg/kg of a 1% solution made by dissolving thiopental powder in a 2:3 H_2O:0.9% NaCl solution) injected intraperitoneally 5 minutes before breathing the 21% O_2 in N_2 mixture for 15 minutes preceding exposure to the hypoxic mixture. This dose was selected because it was that used in the Hartung and Cottrell study (7). Groups 3 and 7 were untreated, but breathed 21% O_2/50% N_2O/N_2 for 15 minutes preceding exposure to the hypoxic mixture which also contained 50% N_2O. Groups 4 and 8 were treated with thiopental (100 mg/kg) 5 minutes before breathing 21% O_2/50% N_2O/N_2 for 15 minutes preceding exposure to the hypoxic mixture containing 50% N_2O.

Groups 9–13 ($n = 64$) were used to study the effect of thiopental dose on survival time (Table 2). Thiopental doses were 50, 60, 70, 80, 90 and 120 mg/kg. These animals were studied in an ambient temperature of 35.5°C. Each was injected with thiopental intraperitoneally 5 minutes before breathing 21% O_2 in N_2 for 15 minutes preceding exposure to the hypoxic mixture. An untreated group (group 9) was studied simultaneously.

The experimental design is shown in Figure 1. For each set of three animals studied, one animal was

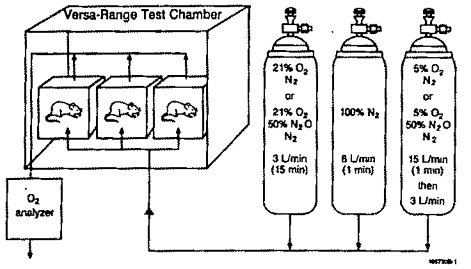
Versa-Range Test Chamber
O_2 analyzer
21% O_2 N_2 or 21% O_2 50% N_2O N_2
3 L/min (15 min)
100% N_2
8 L/min (1 min)
5% O_2 N_2 or 5% O_2 50% N_2O N_2
15 L/min (1 min) then 3 L/min

Figure 1. Diagram of the experimental arrangement. Respiratory gases were mounted in series for rapid adjustment of oxygen concentration and then connected in parallel to the three chambers containing mice, which were mounted inside the versa-range test chamber for strict control of ambient temperature. Both untreated and thiopental-treated mice were studied simultaneously.

randomly placed in each of three airtight, flow-through chambers mounted in parallel and placed in a Versa range test chamber (Blue M, model 1002-8C). This chamber allowed strict maintenance of a selected ambient temperature. For each group of three animals done, untreated and thiopental-treated animals were rotated sequentially among the chambers, and untreated and thiopental-treated animals were studied simultaneously. Animals breathed the control gas (either 21% O_2/balance N_2 or 21% O_2/50% N_2O/balance N_2) flowing at 3 L/min through the chambers for 15 minutes. The gas mixture was then switched to 100% N_2 flowing at 8 L/min for 1 minute and then to either 5% O_2/balance N_2 or 5% O_2/50% N_2O/balance N_2 flowing at 15 L/min for 1 minute and then at 3 L/min for the remainder of the study. Pilot studies had previously determined that these gas mixtures and flows reduced the oxygen concentration within the chambers to 5% within 1 minute. Oxygen concentration in the delivered gas mixtures was determined by Haldane analysis and was 5.00 ± 0.02%. Oxygen concentration within the chambers was measured continuously by a Beckman paramagnetic oxygen analyzer. Ambient temperature within the chambers was measured continuously, but it did not change once the temperature of the Versa test chamber was set. Survival time was defined as the time from initiation of hypoxic gas flow to cessation of respiration.

Mean survival times among groups at each ambient temperature were compared using Student's *t*-test for unpaired data with the Bonferroni correction for multiple comparisons.

Results

Mean survival times of untreated and thiopental-treated mice exposed to the hypoxic mixture containing only O_2 and N_2 (groups 1 and 2) and exposed to 50% N_2O in addition to O_2 and N_2 (groups 3 and 4) in an ambient temperature of 25°C are presented in Table 1 and Figure 2. Untreated animals exposed to 5% O_2 in N_2 (group 1) survived 4.82 ± 0.37 (mean ± SE) minutes. Exposure to N_2O (group 3) did not significantly alter survival time but the variability was greater (6.14 ± 1.10 minutes). However, treatment with thiopental did significantly prolong survival time. Thiopental-treated animals (group 2) survived 11.84 ± 2.21 minutes after exposure to the hypoxic mixture. Exposure to N_2O (group 4) did not alter the increased survival time produced by thiopental (11.59 ± 1.52 minutes).

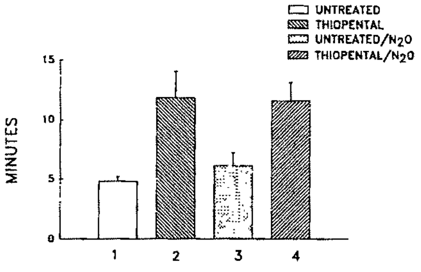

Figure 2. Survival time (mean ± SE) of groups 1–4 exposed to either 21% O_2/balance N_2 before the hypoxic mixture of 5% O_2/balance N_2 (groups 1, 2) or to 21% O_2/50% N_2O/balance N_2 before the hypoxic mixture of 5% O_2/50% N_2O/balance O_2 (groups 3, 4) at an ambient temperature of 25°C. Rectal temperatures in untreated animals averaged 36.5°C, whereas rectal temperatures in thiopental-treated animals averaged 30.4°C.

Rectal temperatures were measured in randomly selected mice. Untreated mice (n = 4) maintained their body temperature at 36.5 ± 0.1°C (mean ± SE), whereas those treated with thiopental (n = 4) had a significant decrease in body temperature to 30.4 ± 0.3°C in the ambient temperature of 25°C during the study period after injection of thiopental. Five additional mice that received 100 mg/kg thiopental intraperitoneally were placed in the chamber with 21% O_2/balance N_2 flowing at 3 L/min at an ambient temperature of 25°C but were not exposed to the hypoxic gas mixture. After the injection of thiopental, their body temperatures decreased from 36.9°C to 30.9°C by 30 minutes, a time roughly equivalent to the period between injection and death in the thiopental-treated animals exposed to hypoxia.

Mean survival times in groups 5–8 studied in an ambient temperature of 35.5°C are presented in Table 1 and Figure 3. Survival time for the untreated group (group 5) was 5.04 ± 0.28 minutes. Exposure to N_2O (group 7) decreased survival time by approximately 20%. Group 7 survived 4.05 ± 0.22 minutes. When the ambient temperature was 35.5°C, high enough to maintain body temperature in the mice, thiopental had no significant effect on survival. Thiopental-

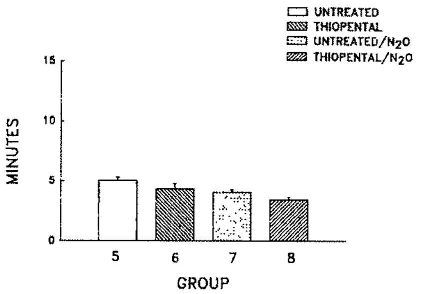

Figure 3. Survival time (mean ± SE) of groups 5–8 exposed to either 21% O_2/balance N_2 before the hypoxic mixture of 5% O_2/balance N_2 (groups 5, 6) or to 21% O_2/50% N_2O/balance N_2 before the hypoxic mixture of 5% O_2/50% N_2O/balance N_2 (groups 7, 8) at an ambient temperature of 35.5°C. Rectal temperature in both the untreated and thiopental treated animals was 36.1°C.

Table 2. Mean Survival Time of Untreated and Thiopental-treated Mice Given Six Different Doses of Thiopental, Both Sets Exposed to 5% Oxygen in Nitrogen at an Ambient Temperature of 35.5°C

Group	*n*	Thiopental dose (mg/kg)	Survival time (mean ± SE) (minutes)
9	9	—	4.49 ± 0.33
10	7	50	4.88 ± 0.86
11	4	60	3.95 ± 0.69
12	6	70	5.31 ± 0.87
13	27	80	5.32 ± 0.38
14	6	90	4.94 ± 0.65
15	5	120	4.67 ± 0.64

treated animals (group 6) survived 4.32 ± 0.44 minutes when exposed to the hypoxic atmosphere. Exposure to N_2O also decreased by approximately 20% the survival time of the thiopental-treated animals. Group 8 survived 3.44 ± 0.22 minutes when exposed to the hypoxic atmosphere. Nitrous oxide lowered the survival time of both untreated or thiopental-treated animals when compared to group 5 (untreated, no N_2O exposure). Body temperature, measured in randomly selected mice, was maintained at 36.1 ± 0.2°C in both untreated ($n = 4$) and thiopental-treated mice ($n = 4$) when the ambient temperature was kept at 35.5°C.

Survival times in an untreated group (group 9) and in groups of mice treated with 50, 60, 70, 80, 90 or 120 mg/kg thiopental (groups 10–15) at an ambient temperature of 35.5°C are presented in Table 2 and Figure 4. These doses of thiopental had no effect on survival time. The untreated group survived 4.49 ± 0.33 minutes. The survival times of the thiopental-treated groups ranged from 3.95 ± 0.69 to 5.32 ± 0.38 minutes. There were no significant differences in survival times among these groups.

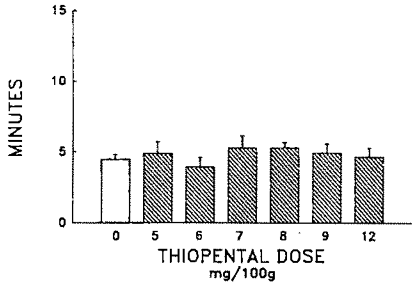

Figure 4. Survival time (mean ± SE) of groups 9–15, which were either untreated (group 9) or treated with varying doses of thiopental before exposure to the hypoxic gas mixture (5% O_2/balance N_2) at an ambient temperature of 35.5°C.

Discussion

Survival times for both untreated animals and thiopental-treated animals at an ambient temperature of 25°C observed in the present study are similar to those reported by Hartung and Cottrell (7). Untreated animals survived 4.8 ± 0.4 minutes in the present study vs 5.2 ± 0.6 minutes in the Hartung and Cottrell study. Thiopental significantly increased survival times an equivalent amount in both studies. Survival time in the thiopental-treated animals was 11.8 ± 2.2 min in the present study and 13.9 ± 2.6 in the Hartung and Cottrell study. Equivalent results from these two studies suggest that they were done in a similar manner; i.e., the studies were conducted in an ambient temperature of approximately 25°C. This can only be assumed because neither ambient temperature nor body temperature was reported in the Hartung and Cottrell study (7). Thiopental abolishes thermoregulation, which was shown in the present study by a significant decrease in body temperature toward ambient temperature in the thiopental-treated mice. The prolonged survival times of 11.8 ± 2.2 minutes (present study) or 13.9 ± 2.6 minutes (7) are similar to the survival time of mice (13.6 ± 1.5 minutes) made hypothermic to 29°C (4). In the original hypoxic mouse study by Arnfred and Secher (1) that reported prolonged survival in hypoxia for thiopental-treated mice (no exact survival times were given), animals were studied in an ambient temperature of 24°C. No body temperatures were reported, but one must assume that these mice became hypothermic, which accounted for the observed prolongation of survival. In subsequent studies, Arnfred and Secher modified their model so that the ambient temperature outside the bottles containing the mice was maintained at 32–34°C (2,9). In these studies the authors reported prolonged survival to 7.95 min for animals treated with thiopental. Again, no body temperatures were reported but body temperature in the barbiturate-treated mice might have decreased 2.5–3.0°C at this ambient temperature during the study period. A decrease in body temperature simply from 37°C to 35°C has been shown to prolong survival by 40% in the hypoxic mouse model (8). Other studies of hypoxia or incomplete global ischemia have reported that mild hypothermia occurs in barbiturate-treated animals but not in untreated animals, and have suggested that this is an important factor in the cerebral protection attributed to the barbiturates (10,11). It has also been reported that hypothermia protects during hypoxia not only by decreasing cerebral blood flow and metabolism but also through a temperature effect on arterial oxygen content and acid/base balance (12). Therefore, it can be concluded that the prolonged survival attributed to thiopental in earlier studies is more likely due to hypothermia than to thiopental. This conclusion is further supported by the observation in the present study that thiopental does not prolong survival in the hypoxic mouse model when body temperature is maintained.

These findings that thiopental prolongs survival only in the presence of hypothermia (but that thiopental promotes hypothermia by abolishing thermoregulation) are in contrast to the results reported by Steen and Michenfelder for pentobarbital (4). That study reported a 390% increase in survival time from 3.8 ± 0.2 to 15.3 ± 1.9 minutes in mice treated with 60 mg/kg pentobarbital. That study was carried out under ambient temperatures of 32–34°C, which pilot studies had demonstrated were adequate to maintain a rectal temperature of 36.0 ± 0.3°C. The difference in survival times between thiopental and pentobarbital suggests that there may be differences among the barbiturates in their ability to provide protection in this model of hypoxia. Possible causes for this difference include differences in the effects of thiopental and pentobarbital on thermoregulation or differences in their ability to depress cardiovascular or respiratory function. Neither cardiovascular nor respiratory function were measured, but a depression of either could have affected survival independent of the barbiturate's effect on cerebral metabolism.

The present study also failed to demonstrate any consistent effect, detrimental or beneficial, of N_2O on survival time. When body temperature was maintained, exposure to N_2O significantly shortened survival in both the untreated (group 7) and thiopental-treated (group 8) groups when compared to the untreated group (group 5) without exposure to N_2O. However, there was no significant difference in survival time when these two groups were compared to groups 1 or 9, which were also untreated, having similar body temperatures. To be detrimental in the presence of hypoxia or ischemia N_2O must either change the oxygen demand/supply ratio or directly interfere with intracellular processes. Nitrous oxide has been reported to affect cerebral blood flow (CBF) and metabolism, but its effects are species-specific. This difference may be due to differences in N_2O potency among species. Nitrous oxide causes the greatest increase in CBF and metabolism in dogs (13–15) in which the MAC of N_2O is 188%. Therefore, studies done in dogs with 50–70% N_2O represents less than 1/2 MAC anesthesia and may be accompanied by a hypermetabolic state due to the stress response associated with increased circulating levels of catecholamines. Several studies in rats report that N_2O has no significant effect on either cerebral blood flow or cerebral metabolism (16–18). Cerebral glucose utilization is similar in both unanesthetized (18) and paralyzed N_2O-ventilated rats (19). Anesthetic agents have been shown to produce prolonged survival in the hypoxic mouse model (3) through a mechanism of decreased cerebral metabolism (3,9). Therefore, in mice (assuming they are similar to rats) N_2O would be predicted to have neither a protective nor a detrimental effect on survival because it has little effect on cerebral metabolism. This lack of effect on N_2O on neurologic outcome has also been shown in the rat (20) in which the addition of N_2O to either isoflurane or halothane anesthesia did not worsen outcome.

The variable to which the hypoxic mouse model remains the most sensitive is the FI_{O_2}. Small changes in FI_{O_2} (<0.005) can markedly affect the survival time of thiopental-treated animals while having no effect on untreated animals (8). For this reason, untreated animals must be studied simultaneously with treated animals exposed to the same environment, same gas flows, and same equilibration times (time to washout 21% O_2 gas mixture to attainment of exactly 5% O_2 in the chamber). Failure to study mice simultaneously in the Hartung and Cottrell experiment (7) may not have controlled for subtle but systematic changes in FI_{O_2}, such that N_2O appeared to reverse the prolonged survival from hypothermia attributed to thiopental.

The present study concludes that neither thiopental nor N_2O have any effect on survival in the hypoxic mouse model, but that hypothermia resulting from low ambient temperature and thiopental's interference with thermoregulation does prolong survival.

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Effects of Nonvolatile Agents on Oxygen Demand and Energy Status in Isolated Hepatocytes

Gerald L. Becker, MD

BECKER GL. Effects of nonvolatile agents on oxygen demand and energy status in isolated hepatocytes. Anesth Analg 1988;67:923–8.

The role of hepatic energy deficits in the pathogenesis of anesthetic hepatotoxicity is suggested by the involvement of hypoxia in various animal models and by the ability of anesthetics to inhibit mitochondrial oxidations. We have been studying anesthetic effects on hepatocellular energy metabolism using suspensions of intact hepatocytes freshly isolated from phenobarbital-treated or untreated rats (+PB or −PB cells, respectively), an experimental system that is metabolically complete yet also biochemically homogeneous and accessible. In the present work, diazepam, lidocaine, thiopental, and enflurane, as well as the combination of thiopental and enflurane, were studied at concentrations similar to those achieved in vivo. Thiopental increased cellular oxygen consumption rate (VO_2) in both +PB and −PB cells significantly, as did aminopyrine, a test substrate for PB-inducible cytochrome P450 activity. Diazepam increased VO_2 only in +PB cells, as did enflurane, whereas lidocaine did not increase VO_2 in either +PB or −PB cells. The combination of thiopental and enflurane significantly decreased VO_2 in −PB cells but increased it in +PB cells. The higher VO_2 in +PB cells compared to −PB cells, seen with all drugs tested (except lidocaine), was eliminated by prior addition of the P450 inhibitor metyrapone.

Starting from steady states of oxygen metabolism, with VO_2 offset by O_2 supply from an overlying gas phase and Po_2 stabilized at 24 mm Hg, aminopyrine significantly lowered extracellular Po_2, increased lactate production, and decreased high energy phosphate levels within 10 minutes. These changes in energy status were limited to +PB cells and were largely prevented by running incubations at higher Po_2 levels (>20 mm Hg throughout), suggesting that hypoxia due to P450-mediated VO_2 increased had been mainly responsible. On the other hand, in contrast to either drug alone, the combination of thiopental and enflurane produced statistically significant hepatocellular energy impairment that was seen even in −PB cells; this impairment could not be reversed at higher Po_2, a finding that is consistent with direct inhibition of the mitochondrial respiratory chain. These results support the possibility that with increases in oxygen demand (P450 induction), decreases in oxygen supply (hypoxia), and/or other agents present with interacting effects on oxygen-supported metabolism, drugs and doses that are considered safe during anesthesia might nonetheless promote hepatocellular energy deficits as a result of hypoxic or nonhypoxic mechanisms.

Key Words: ANESTHETICS, VOLATILE—enflurane. ANESTHETICS, INTRAVENOUS—thiopental. ANESTHETICS, LOCAL—lidocaine. COMPLICATIONS—hepatotoxicity. HYPNOTICS, BENZODIAZEPINES—diazepam. LIVER—hepatotoxicity.

Most oxygen consumed by body tissues supports mitochondrial respiratory chain oxidations, which are coupled to the formation of adenosine triphosphate (ATP) essential to cellular function and viability. In isolated mitochondria, a variety of anesthetics are able to inhibit these oxidations (see Reference 1 for review) as well as ATP formation (2). The possibility that energy deficits could be produced in vivo by this mechanism and thereby contribute to anesthetic hepatotoxicity is reinforced by the finding that hypoxia, which also inhibits mitochondrial energy generation and promotes energy deficits (3), is involved in the pathogenesis of hepatic injury caused by anesthetics in laboratory animals (see References 4–6 for review).

However, this hypothesis regarding the effects of

Received from the Department of Anesthesiology, University of Nebraska Medical Center, Omaha, Nebraska. Accepted for publication May 17, 1988.

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Preliminary experiments for this study were performed in the Department of Anesthesiology, Michael Reese Hospital and Medical Center, Chicago, Illinois, and were presented at the 1987 annual meeting of the American Society of Anesthesiologists, Atlanta, Georgia.

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anesthetics on hepatocellular energy status, and other hypotheses concerning biochemical effects of anesthetics (with additional implications for anesthetic hepatotoxicity), remains inadequately tested because existing whole organ/animal systems are too complex and heterogeneous to provide clearcut evidence concerning biochemical events at the (sub)cellular level, where injury actually occurs (7). Recent work on mechanisms of anesthetic hepatotoxicity at the cellular level has turned to isolated hepatocytes as an experimental system sufficiently intact to give physiologically accurate metabolic responses, yet amenable to study in a biochemically uniform environment with improved control or elimination of confounding variables (8–12).

Our work on interactions of anesthetics with energy metabolism in isolated hepatocytes has focused on the fact that many drugs used in anesthesiology are extensively degraded in the liver via the cytochrome P450 (mixed function oxidase) enzyme system (13–15). Most of such reactions are oxidative, consuming two oxygen atoms for each molecule of drug metabolized. We found that 1 minimum alveolar concentration (MAC) halothane or enflurane significantly increased oxygen consumption rates (VO_2) in hepatocytes isolated from phenobarbital-treated rats (+PB cells) but not in hepatocytes from untreated rats (−PB cells). The increases in VO_2 in +PB cells were prevented by P450 inhibitors (16), indicating that differences in P450 activity were responsible for the extra oxygen consumption. Under simulated tissue conditions, with baseline oxygen demand by the cells offset with oxygen supplied by diffusion from an equilibrating gas phase, the increases in VO_2 forced extracellular Po_2 to decrease from an initial value of 24 mmHg to a final value <10 mmHg within 10 minutes after addition of anesthetic to the gas phase. Impairment of mitochondrial energy generation was confirmed by increased lactate production, and energy deficits by a decreased ratio of adenosine triphosphate to adenosine diphosphate (ATP/ADP). The −PB cells showed neither of these changes in energy status.

Based on the results described above, we concluded that volatile anesthetics produced energy deficits preferentially in +PB hepatocytes through accelerated rates of aerobic metabolism of anesthetic, a process that effectively competed with mitochondrial oxidative phosphorylation for available oxygen. In principle, any other factors able to influence oxidative drug metabolism or to otherwise affect intrahepatic oxygen balance would also have the potential to alter oxygen and energy metabolism in liver cells. In the present work, some of those other factors—nonvolatile agents, combinations of drugs, and shifts in extracellular Po_2 values—have also been examined for their ability to affect hepatocellular oxygen metabolism and energy status.

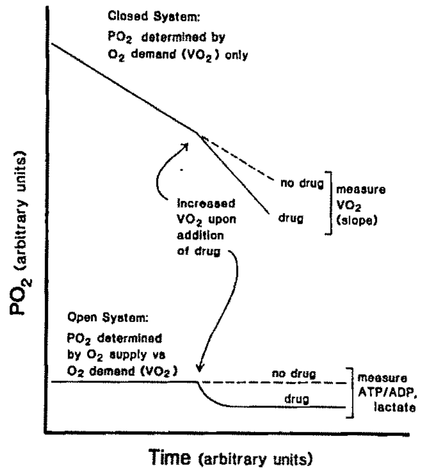

Figure 1. Schematic diagram of Po_2 changes occurring during addition of drug to hepatocyte suspensions. Time courses of open and closed system incubations are plotted on the same time axis, with addition of drug at the same time point, to facilitate comparison of Po_2 responses in the two different systems.

Methods

Hepatocytes were isolated from rats and experimental incubations carried out as previously described (4,5). Protocols were approved by the institution's animal experimentation review committee. Oxygen metabolism was studied at 37°C in a 1.8-ml chamber with a built-in O_2 electrode continuously monitoring extracellular Po_2 in the cell suspension (liquid phase). This apparatus was used in two configurations to carry out two different kinds of incubations. By filling the chamber completely with liquid phase (at 3 to 4 million cells/ml) and sealing it (to form a closed system), rates of O_2 consumption (VO_2) were directly measurable as the slope of the recording of Po_2 versus time, as diagrammed in the upper portion of Figure 1.

An alternative, open-system approach was used to assess the impact of VO_2 changes on hepatocellular energy metabolism under more realistic physiological conditions. Steady states of oxygen metabolism were achieved by leaving the chamber partially filled (1.2-ml liquid phase with 10 million cells/ml) and continuously circulating fresh O_2-containing gas phase through the unoccupied volume (0.6 ml) above the cell suspension. Under the latter conditions, as diagrammed in the lower portion of Figure 1, an increase in VO_2 shifted the system to a new steady state of

Table 1. Rates of Oxygen Consumption (VO_2) after drug addition to Suspensions of Isolated Hepatocytes (closed system)

	VO_2 (%baseline)		
Drug (concentration)	−PB	+PB	+PB, +MP
Aminopyrine (0.25 mM)	112 ± 9[a]	128 ± 7[a]	102 ± 4
Diazepam (2 μg/ml)	100 ± 6	109 ± 6[a]	100 ± 6
Lidocaine (5 μg/ml)	100 ± 7	104 ± 6	99 ± 5
Thiopental (50 μg/ml)	107 ± 8[a]	127 ± 8[a]	97 ± 8
Enflurane (8 mg/ml)	97 ± 6	127 ± 6[a]	93 ± 7
thiopental (μg/ml) + enflurane (8 mg/ml)	87 ± 5[a]	113 ± 5[a]	85 ± 6[a]

Values given are means ± SEM of 12 to 24 different preparations. −PB or +PB: cells isolated from untreated or PB-treated rats. +MP: metyrapone 0.25 mM added before drug.

[a] $P < 0.05$ vs. baseline value (no drug added).

oxygen metabolism at a lower value of Po_2. Ten minutes after test drugs were added, the incubation was acid-quenched, extracted, and analyzed for ATP, ADP, and lactate concentrations as previously described (11). As before, the ATP/ADP ratio was used as a sensitive indicator of the overall balance between high energy phosphate supply and demand (2,11). Changes in lactate levels between zero and 10-minute time points (Δlactate) measured the extent to which anaerobic energy metabolism (glycolysis) had occurred during that period, reflecting the inability of aerobic energy metabolism (oxidative phosphorylation) to meet hepatocellular energy needs.

Each drug to be tested was added at a concentration representative of that achieved in plasma during clinical use. Results were analyzed by using the paired student's *t* test to compare VO_2 before and after addition of drug to a given incubation in the closed system (16). The same paired analysis was used to compare Po_2, ATP/ADP, and Δlactate values obtained from open-system incubations in the absence (control) and presence of drug. Because accurate metabolite analyses required quenching of the entire sample, comparison of control and test conditions required two separate incubations/aliquots. When these were drawn from the same bulk preparation, paired analysis was helpful in eliminating differences in metabolic baselines among preparations (11). $P < 0.05$ was considered statistically significant.

Results

Table 1 shows VO_2 changes in the closed system upon introduction of the drugs studied at the concentrations given in parentheses. Saturating concentrations of aminopyrine (250 μM), considered a model substrate for phenobarbital-inducible P450 (7), increased VO_2 by 28% in +PB cells and by 12% in −PB cells. Comparable increases in VO_2 were also seen with thiopental (50 μg/ml) in both +PB and −PB cells. Diazepam (5 μg/ml) and enflurane (8 mg/ml) increased VO_2 only in +PB cells, whereas lidocaine (2 μg/ml) produced no increase in either group. As observed with volatile agents in the previous study (16), the VO_2 values in +PB cells could be abolished by adding the P450 inhibitor metyrapone, which did not by itself affect VO_2.

Table 2 shows how some of those same drugs affected hepatocellular energy status under steady-state conditions (open system). As diagrammed in Figure 1 and demonstrated previously for the halogenated volatile anesthetics (16), VO_2 increases, which occurred upon addition of the drug, were manifested as decreases in steady-state Po_2 in the open system. In the present study, the VO_2 increases (Table 1) and associated Po_2 decreases (Table 2) produced by aminopyrine in +PB cells gave rise to both increased Δlactate and decreased ATP/ADP when incubations were initiated from a baseline of Po_2 = 24 mmHg. A lesser change—increased Δlactate only—was seen in +PB cells when initial Po_2 was set high enough (120 mmHg) to keep $Po_2 > 20$ mmHg at all times throughout the incubation, thereby preventing hypoxia. When −PB rather than +PB cells were used, aminopyrine addition produced no significant change in either measure of energy status.

Thiopental alone affected only Δlactate and did so only in +PB cells and only at the lower initial Po_2 value. Enflurane alone at 0.5 MAC produced no significant hepatocellular energy changes under any set of conditions, a finding that is consistent with previous results (16). However, those same levels of thiopental and enflurane, when added together to the same incubation, significantly decreased ATP/ADP in +PB cells and increased lactate in both +PB and −PB cells. Furthermore, these changes were noted at the higher as well as the lower ranges of Po_2 values.

Discussion

The results described above have further delineated biochemical interactions of anesthetics with hepatocellular oxygen balance and energy metabolism. In this and other studies from this laboratory (11,16), particular attention has been given to the impact of drug metabolism occurring in both normal and P450-induced states. The present work shows that agents

Table 2. High Energy Phosphate Levels (ATP/ADP) and Lactate Production (ΔLactate) after Drug Addition to Isolated Hepatocytes (Open System)

	Initial	Final Po_2 (mm Hg)		ATP/ADP (% control)		Δlactate (Control = 0) (nmol/10^7 cells)	
Drug	Po_2 (mm Hg)	−PB	+PB	−PB	+PB	−PB	+PB
Aminopyrine	24	15 ± 5^a	5 ± 3^a	95 ± 6	86 ± 8^a	37 ± 36	125 ± 66^a
	120	81 ± 8^a	41 ± 6^a	103 ± 9	87 ± 6	19 ± 37	87 ± 64^a
Thiopental	24	19 ± 5	8 ± 4^a	95 ± 8	91 ± 9	5 ± 26	55 ± 50^a
	120	93 ± 10^a	48 ± 9^a	106 ± 11	104 ± 13	25 ± 30	31 ± 52
Enflurane	24	27 ± 4	10 ± 3^a	104 ± 15	100 ± 13	62 ± 32	7 ± 59
	120	125 ± 9	52 ± 5^a	96 ± 11	96 ± 11	77 ± 50	−32 ± 53
Thiopental	24	34 ± 6^a	16 ± 3^a	79 ± 7	75 ± 9^a	71 ± 56^a	87 ± 64^a
+ enflurane	120	142 ± 16^a	93 ± 8^a	83 ± 7	80 ± 8^a	100 ± 56^a	45 ± 51^a

n = 12 to 16 for each group; other footnotes same as for Table 1.

other than the volatile anesthetics studied previously (16) can also bring about significant net increases in VO_2 as a result of the metabolism of the drugs in liver cells; therefore, such increases in VO_2 cannot be dismissed as a unique and possibly artifactual effect of the halogenated inhalation anesthetics. The increases in VO_2 observed in isolated rat hepatocytes in this study are similar to those reported for isolated perfused rat liver under similar experimental conditions, such as prior induction with phenobarbital in vivo, and acute exposure to pentobarbital in vitro (17).

In contrast to the volatile anesthetics studied previously, some of the nonvolatile drugs used in this study increased VO_2 in −PB as well as +PB cells. The latter would in fact be the more typical with substrates for the P450 system. Even without prior P450 induction, a broad range of compounds can be metabolized by baseline levels of constitutive P450 isozymes (18); the more rapid of those basal rates might be expected to produce net increases in VO_2. Volatile anesthetics are known to have an additional, opposing effect on hepatocellular VO_2: they diminish VO_2 by inhibiting mitochondrial oxygen utilization. Depending on potency and concentration, they inhibit electron transport directly at site 1 of the respiratory chain (1,19) and/or indirectly by reducing cellular energy demand (16,20). In −PB cells, with their low basal P450 activities, the inhibitory effects of the volatile agents prevailed, so that VO_2 decreased in net fashion (16). This interpretation is supported by the fact that addition of metyrapone, which is known to selectively inhibit P450 activity, converted the VO_2 increase in +PB cells into a net decrease in VO_2 similar to that observed in −PB cells, as shown in Table 1 (16).

In the present study, hypoxia and its contribution to energy deficits were eliminated in selected open system incubations by starting them at Po_2 of 120 mmHg. In those incubations, even with relatively large increases in VO_2 due to accelerated drug metabolism (in +PB cells with actively metabolized P450 substrates), all Po_2 values remained > 20 mmHg (Table 2) and thus above the hypoxic range. Incubating +PB cells at higher Po_2s eliminated the increases in Δlactate with thiopental and the decreases in ATP/ADP with aminopyrine that occurred at the lower levels of Po_2. Presumably, then, hypoxia produced by P450-mediated increases in VO_2 were responsible for these changes in hepatocellular energy status.

On the other hand, none of the changes in energy metabolism produced by the combination of thiopental and enflurane at lower Po_2 were prevented by conducting the same incubations at higher Po_2 levels. This finding indicates that oxygen lack was not responsible for those changes. A qualitatively different mechanism for development of energy deficits when the two drugs were present together is also suggested by the fact that VO_2 decreased rather than increased. Like the halogenated anesthetics, barbiturates also inhibit oxygen utilization arising from cellular energy demand and mitochondrial energy generation (21,22). Since such inhibition is not competitive with oxygen, lack of its reversal by higher Po_2 levels is to be expected. Nor is it surprising that +PB and −PB cells were comparably affected, since with electron flow in the respiratory chain already inhibited at an "upstream" site by the anesthetics, oxygen deficits due to increases in VO_2 in +PB cells may not have been able to further restrict electron flow "downstream" and thereby worsen energy deficits (2,3).

Another notable finding in liver cells exposed in this study to the combination of volatile plus nonvolatile anesthetics was the magnitude of the energy deficits produced—greater than would have been predicted from the separate effects of the two drugs. Individual anesthetics at clinical by effective levels might produce subthreshold inhibition of energy production so that the effects become detectable only when the drugs are used in combination. This possibility is supported by findings that individual volatile agents or barbiturates also impaired energy status at tissue levels corresponding to 2 to 3 MAC (16,20,23).

While direct or indirect inhibition of mitochondrial energy generation may account for the energy deficits at higher $\mathrm{Po_2}$ levels produced in liver cells by anesthetics, the ability of aminopyrine to promote lactate production in +PB cells at higher $\mathrm{Po_2}$ levels requires a different explanation. One possibility is that rapid rates of P450-mediated drug metabolism may have triggered metabolic shifts other than those so far discussed. In addition to oxygen and the drug itself, oxidative drug metabolism also consumes a third substrate in stoichiometric amounts, namely the reduced form of nicotinamide adenine dinucleotide (NADPH). In other metabolic situations with increased NADPH demands, intermediates of the citrate cycle can be diverted to serve as substrates in (cytoplasmic) reactions generating NADPH as a product (24,25). The ensuing depletion of citrate cycle intermediates make their concentration(s) limiting to the overall rate of mitochondrial respiration and ATP generation (26). Further experiments will be necessary to confirm this possibility under the conditions of the present study.

In summary, at levels comparable to those attained in vivo, various nonvolatile agents were oxidatively metabolized at rates that substantially increased $\mathrm{VO_2}$ in +PB cells, with lesser increases in −PB cells. Under steady states of O_2 metabolism simulating tissue conditions, hypoxia ($\mathrm{Po_2} < 10$ mm Hg, or increased Δlactate) and energy deficits (decreased ATP/ADP) developed more readily in +PB than in −PB cells. In contrast to either drug alone, the combination of enflurane plus thiopental produced hepatocellular energy deficits that were statistically significant in both +PB and −PB cells and could not be reversed by increased availability of oxygen. The use of multiple drugs in anesthetic management may increase the possibility of hepatocellular energy deficits via hypoxic mechanisms (P450-mediated increases in $\mathrm{VO_2}$), nonhypoxic mechanisms (respiratory chain inhibition), or a combination of both. The clinical significance of effects on hepatocellular energy status identified in the present work will have to be verified in more intact systems that include extracellular homeostatic mechanisms for maintaining oxygen and energy balance.

The author is grateful for the expert assistance of Audrey Holland and Pamela Reilly in the laboratory and Beverly Christensen in the office.

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Sixty-Three Years Ago In

Anesthesia & Analgesia

G. Labat: Anesthesia—the predominant element in surgery. Current Researches in Anesthesia & Analgesia 1925;4:29–35.

This paper represents the presidential address at a joint meeting in New York City of the American Society of Regional Anesthesia (ASRA in today's incarnation) and the Eastern Society of Anesthetists (soon to become defunct). Gaston Labat, president of ASRA in 1925, was a pioneer in the development, refinement, and standardization of regional anesthetic techniques. His book on regional anesthesia is still a classic. Regional anesthesia was in its heyday in the 1920s partly because of Labat's efforts, but his efforts were aided and abetted by the fact that ether and nitrous oxide, alone or in combination, were the only alternatives. These anesthetics had severe inherent limitations that were accentuated by the primitive equipment available for their administration and the low level of training and skill on the part of those administering them. Labat developed regional anesthesia as a safe, reliable, effective, and very welcome alternative to ether and nitrous oxide. While acknowledging that there really may be times when inhalation anesthesia may be indicated, Labat makes a strong case for regional anesthesia in this presentation. He makes a particular point of its value in view of Crile's recent introduction of the theory of anociassociation, a theory attributing shock and other adverse responses during surgery to afferent pain impulses arising in the surgical field. Block these pain impulses, Crile said, and patient mortality and morbidity decrease. Labat also suggests in this talk that "surgical technique has almost reached the limit of refinement," an astonishing view of the future by one so talented, though he certainly has much company, past and present, in the parochial belief that the present represents the extent of man's future. Labat goes on to comment that "asepsis needs no further development" and "results [now] depend on methods of treatment and individual skill in applying them." Implicit is the concept that the only way to advance surgery is for surgeons to develop skill in applying regional anesthesia. Yes, surgeons, not anesthetists. "The surgeon must know the pharmacologic and physiologic properties of the drugs he (sic) is using" for regional anesthesia because it is usually surgeons, not anesthetists, who administer regional anesthesia to the patients they are about to operate on. So rare was anyone in 1925 other than a surgeon skilled in regional anesthesia that, from a practical point of view. Labat had to sell regional anesthesia to surgeons, not anesthetists, of whom there were so few. The title of his talk, "Anesthesia—the predominant element of surgery," places anesthesia as an element, a part of surgery, not a separate and distinct clinical discipline, which is an attitude that still persists in the minds of some.

ANESTH ANALG
1988;67:929–35

Functional and Metabolic Effects of Bupivacaine and Lidocaine in the Perfused Working Rat Heart

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CRONAU LH, Jr., MERIN RG, ABOULEISH E, STEENBERG M, MELGAREJO AB. Functional and metabolic effects of bupivacaine and lidocaine in the perfused working rat heart. Anesth Analg 1988;67:929–35.

The effects of bupivacaine (2.5, 5, 10, and 12.5 mg/L) and lidocaine (12.5, 25, 40, and 50 mg/L), on spontaneous heart rate, mean pressure development, cardiac output, and coronary flow were compared after 15 minutes' exposure in the isolated perfused working rat heart preparation. In addition, myocardial oxygen consumption, glucose utilization, lactate production, tissue content of glycogen, adenine nucleotides, and creatine phosphate content were measured. The relative potency of bupivacaine to lidocaine, calculated from slopes of regression equations, as indicated by the four mechanical variables and oxygen consumption, was 4.59. When the bupivacaine concentration was "normalized" using this value, bupivacaine and lidocaine showed indistinguishable effects on glucose utilization, lactate production, and tissue glycogen. Neither of the local anesthetics had any influence on energy charge or creatine phosphate content.

Key Words: ANESTHETICS, LOCAL—bupivacaine, lidocaine. HEART, MYOCARDIUM—metabolism, function. TOXICITY—bupivacaine, lidocaine.

The relative toxicities of bupivacaine and lidocaine have created controversy and differing opinion regarding the safety and merits of using the former drug (1,2). The toxicity of the two drugs has been compared in vivo in dogs (3,4), sheep (5), cats (6), rats (7), pigs (8), and in vitro using guinea pig papillary muscle (9), isolated guinea pig atria (10), and the Langendorff heart preparation of the guinea pig (11) and rabbit (12).

In the in vivo studies in the dog, sheep, cats, and pigs, the acute cardiovascular toxicity ratio of bupivacaine/lidocaine ranged from 2.71:1 to 16:1 (3,5,6,8). Tanz et al. (11), using the guinea pig Langendorff heart preparation, found that bupivacaine was tenfold more cardiodepressant than lidocaine. Lynch (9), using guinea pig papillary muscle, found that the relative molar depressant effect of bupivacaine to lidocaine to be approximately 10:1.

The present study was undertaken to compare the mechanical and metabolic effects of bupivacaine and lidocaine in the isolated working rat heart preparation (13). This technique eliminates confounding neurohumoral effects of in vivo studies and may possibly show differences in metabolism as a contributory mechanism of toxicity in the functioning myocardium.

Methods

Male Wistar rats, weighing 250–275 g, were fed *ad libitum* until the experiment began. The animals were given 1000 units of intraperitoneal porcine heparin 15 minutes before they were anesthetized with sodium pentobarbital (30 mg) by the same route.

The hearts were removed and mounted in a perfusion apparatus as described by Morgan et al. (13), and studied at 37°C (maximum deviation ± 0.4°C) measured from the surface of the ventricle with a calibrated thermistor. The hearts were perfused as a Langendorff preparation at approximately 60 cm H_2O pressure with a modified Krebs-Henseleit solution containing 10 mM glucose to which 10 mU/ml of insulin was added when desired. After this preliminary perfusion, the heart was converted to working preparation by perfusing the left atrium and releasing the aortic outflow for a stabilization period of approx-

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Received from the Department of Anesthesiology, University of Texas Medical School at Houston, Houston, Texas. Accepted for publication May 16, 1988.

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imately 10 minutes without recirculation of aortic output. The perfusion fluid containing 2-[^{3}H]glucose was provided by a glass oxygenator-reservoir. Left atrial pressure was maintained at 10 cm H_2O. The experimental period was then begun by recirculating the aortic output. This experimental period consisted of two 15-minute segments. In the first, only labeled glucose was present. In the second, initiated by changing to a second glass oxygenator-reservoir by means of a three-way stopcock, local anesthetic was added (except for control studies) in addition to the labeled glucose. Experiments were terminated at the end of the 30-minute experimental perfusion period by freeze-clamping the heart as it was beating. Mean pressure generated at the end of the 30 minutes, just before freeze-clamping, was at least 90% of the zero time experimental period value in the case of the control heart. Although temporal effects could be present, it was assumed that such effects would apply in an unbiased manner to all conditions of anesthetic concentration. The local anesthetics were added to obtain concentration ranges of 12.5 to 50 mg/L for lidocaine and 2.5 to 12.5 mg/L for bupivacaine.

The apparatus included a glass oxygenator through which 95% O_2–5% CO_2 was introduced. Aortic oxygen tension was estimated by sampling perfusate from a three-way stopcock on the left atrial line with a gas-tight syringe. For measurement of oxygen tension of coronary effluent, a catheter was placed in the pulmonary artery, from which samples were obtained with a gas-tight syringe. The oxygen tension was measured in a Corning Model 1303 blood gas analyzer calibrated according to the manufacturer's specifications before the experiments. The calibration and corrections to observed values were made by independent tonometry according to NCCLS document No. C27-P (14).

Aortic pressure was recorded via a Statham 23-dB strain gauge transducer on a Hewlett-Packard polygraph. Coronary flow was measured by timed collection of the pulmonary artery outflow and surface runoff of the heart resulting from coronary sinus and Thebesian vessel drainage. The cardiac output was measured by timed collection of the aortic outflow plus the coronary effluent rates. Mechanical events were tabulated at the time of fluid sampling. At no time was the coronary effluent recirculated.

Aliquot fractions of coronary and aortic effluent were taken during the 28- to 30-minute interval of the experimental period. Pulmonary arterial samples (coronary effluent) for estimates of lactate production and glucose utilization were obtained during the same interval. Glucose uptake was estimated by the appearance of ^{3}HOH from 2-[^{3}H]glucose (15). One-half milliliter of aortic or coronary effluent was passed over Dowex resin columns and washed with four 0.2-ml amounts of distilled water. The entire column wash was counted in the liquid scintillation counter. Glucose utilization was estimated by the appearance of tritiated water. Lactate in the effluent was assayed by enzymatic methods (16).

At the end of the experimental period, most ventricles were freeze-clamped. The tissue was extracted with cold perchloric acid, neutralized with KOH, and assayed by enzymatic methods for glycogen (17). Additional extract was assayed by HPLC for adenine nucleotides and creatine phosphate (18). Data to estimate the wet ventricular weight as function of body weight were obtained from 123 animals of these and other studies. Not all hearts yielded all biochemical assays. It was not necessary to discard any data because of outlying values. The numbers shown in the tables indicate the number of hearts used for any given regression. Any given heart provided data for only one condition of local anesthetic—eg, 12.5 mg/L bupivacaine, no insulin; control, no insulin.

Data were analyzed by using a commercially available statistical system (19). The significance of the regression, $r = 0$, was determined by analysis of variance (ANOVA). The effect of lidocaine and bupivacaine could not be compared with two-way ANOVA, but their regressions could be compared with ANOVA (20). The P values are provided in the text and/or tables. Values greater than 0.05 were considered nonsignificant. For illustrative purposes, 95% confidence intervals were constructed (21). The ANOVA was used to test the significance of energy charge and creatine phosphate concentration. The Student's t test was used to indicate significance of creatine phosphate data.

Results

Cardiac Function and Oxygen Consumption

Insulin, in the presence of lidocaine or bupivacaine, had no significant modifying effect on heart rate, mean pressure development, cardiac output, coronary flow, nor myocardial oxygen consumption. Lidocaine significantly depressed heart rate, mean pressure development, cardiac output, coronary flow, and myocardial oxygen consumption in a dose-related manner ($P < 0.0005$ for ANOVA of the regressions of each). Bupivacaine had equally significant effects on these same parameters. The regression constants are shown in Table 1. The difference in

Table 1. Dose Relationships of Local Anesthetics, in Terms of Effects on Cardiac Function and Oxygen Consumption in the Perfused Working Rat Heart

Variable	Anesthetic	Intercept	Slope	S_b/S_l
Heart rate (beat/min)	L (118)	245.70	−2.53	5.49
	B (126)	245.45	−13.90	
Mean pressure (mm Hg)	L (118)	82.54	−0.75	4.07
	B (126)	82.27	−3.05	
Cardiac output (ml/g wwt/min)	L (118)	53.32	−0.43	4.91
	B (126)	53.14	−2.11	
Coronary flow (ml/g wwt/min)	L (118)	15.62	−0.17	4.35
	B (126)	14.96	−0.74	
Oxygen consumption $\frac{\mu\text{mol}}{(\text{g wwt})(\text{min})}$	L (114)	7.76	−0.09	4.11
	B (126)	7.66	−0.37	

Because insulin had no measurable influence, the data were pooled. The total number of points used to construct the regression is shown (n) as well as the relative potency of the drugs (S_b/S_l).

L = lidocaine; B = bupivacaine.

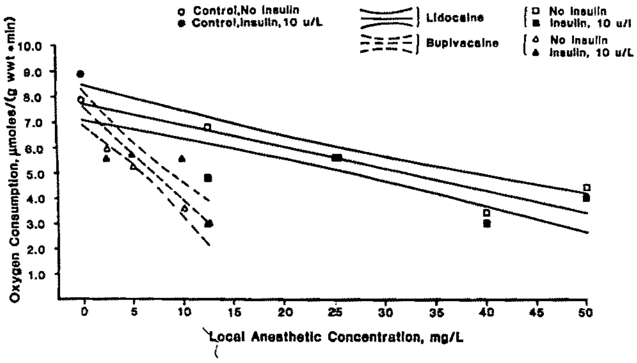

Figure 1. Regression equations for bupivacaine and lidocaine influence on myocardial oxygen consumption with 95% confidence boundaries. Constants for the equations are shown in Table 1. Significance of comparison are presented in the text.

relative potency is apparent and the regressions were significantly different for all five functional variables ($P < 0.0005$ for each). The relative potency of bupivacaine compared to lidocaine, as expressed by a ratio of their slopes, ranged from approximately 4 to 5.5 with a mean of 4.59. For illustrative purposes, the data for local anesthetic effect on myocardial oxygen consumption are plotted in Figure 1.

Glucose Metabolism

Table 2 summarizes the resultant data of glucose metabolism in the form of regression analysis. For illustrative purposes, the data for glucose uptake are plotted in Figure 2. Consider the data obtained in the absence of insulin. The ANOVA comparison of the regressions for glucose uptake and lactate production, in the absence of insulin, indicated that bupivacaine had no influence. On the other hand, lidocaine exerted a significant influence on both glucose uptake and lactate production in the absence of insulin. The ANOVA comparison of the two lactate production regressions indicates no significant difference between the two local anesthetics. These latter disparate results may be related, in part, to the small slopes which were observed and associated 95% confidence intervals, −0.007 ± 0.005 and −0.011 ± 0.033 for lidocaine and bupivacaine, respectively. That is, the latter confidence interval enclosed the former. In the absence of insulin, lidocaine and bupivacaine had significantly different regressions for tissue glycogen. Only bupivacaine showed a significant effect on tissue glycogen.

In the presence of insulin, 10 mU/ml, lidocaine and bupivacaine showed significant depressant effects on glucose uptake and lactate production, and were significantly different in the magnitude of their effects. Although lidocaine showed a significant influence on tissue glycogen, the lidocaine and bupivacaine data could not be distinguished with ANOVA. As similar to the circumstance described above, the slopes for lidocaine and bupivacaine effect on glycogen, with 95% confidence intervals, were 0.944 ± 0.723 and 1.689 ± 2.060, respectively.

In summary, in the presence of insulin, both local anesthetics depressed glucose uptake and lactate production in a dose-related manner. However, these agents were significantly different from each other. In the absence of insulin, the depressant effect of lidocaine, but not bupivacaine, was evident on glucose uptake and lactate production. In the presence of insulin, lidocaine, but not bupivacaine, was positively associated with tissue glycogen stores. When the concentration of bupivacaine was multiplied by 4.59, the regressions for the effects of lidocaine and bupivacaine, for glucose uptake, lactate production, and tissue glycogen stores were indistinguishable when compared with ANOVA, either in the presence or absence of insulin.

High Energy Phosphate

Two-way ANOVA showed that neither local anesthetic nor insulin influenced nucleotide concentration or energy charge. Neither anesthetic had a significant influence on creatine phosphate content, nor did they modify significant insulin-associated increase of creatine phosphate. Thus, the anesthetics had no influence on the high energy phosphates. The data are shown in Table 3.

Table 2. Effects of Lidocaine (L) and Bupivacaine (B) on Myocardial Glucose Metabolism

Variable	Anesthetic	Intercept	Slope	$r = 0$	L vs. B
	No insulin				
Glucose uptake, μmol/g wwt/min	L (57)	1.178	−0.007	<0.025	<0.05
	B (59)	1.053	−0.023	NS	
Lactate production, μmol/g wwt/min	L (57)	0.656	−0.007	<0.05	NS
	B (61)	0.550	0.011	NS	
Tissue glycogen, μmol/(g protein)	L (39)	18.483	0.208	NS	<0.025
	B (40)	14.030	1.187	<0.005	
	Insulin (10 mu/ml)				
Glucose uptake, μmol/g wwt/min	L (54)	2.552	−0.022	<0.0005	<0.0005
	B (58)	2.469	−0.095	<0.0005	
Lactate production, μmol/g wwt/min	L (54)	2.141	−0.021	<0.005	<0.05
	B (58)	1.932	−0.056	<0.025	
Tissue glycogen, μmol/(g protein)	L (32)	66.414	0.944	<0.025	NS
	B (34)	73.379	1.689	NS	

Number of data points (in parentheses), intercept, slope, and significance of ANOVA of regression and $r = 0$, are shown sequentially. L vs. B indicates the statistical significance of differences between L and B by ANOVA.

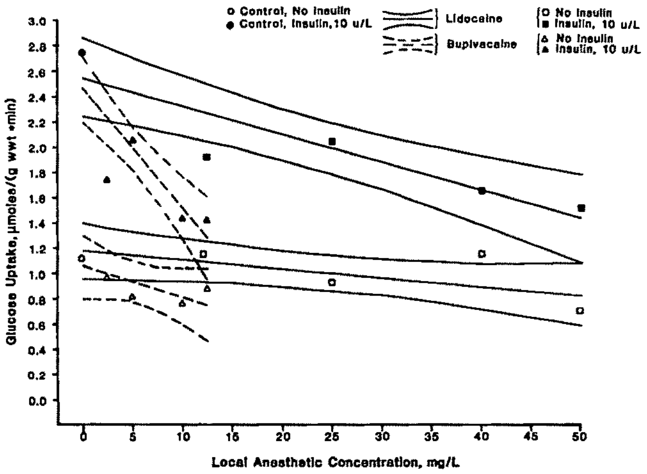

Figure 2. Regression equations for bupivacaine and lidocaine effect on myocardial glucose uptake with 95% confidence boundaries. Statistics are shown in Table 2. Constants for the equation and statistical comparisons are shown in Table 2 with comments in the text.

Discussion

The perfused working rat heart was employed to compare the myocardial toxicity of lidocaine and bupivacaine in the absence of autonomic, acid-base balance, and circulating humoral influences found in vivo. The crystalloid perfusion was adequate for oxygenation, as indicated by the mixed venous oxygen tension that was always greater than 60 mm Hg, with a mean control value of 154 mm Hg (standard deviation 54 mm Hg). Neither in the case of bupivacaine nor lidocaine was there a significant influence on mixed venous oxygen tension when analyzed with ANOVA. Furthermore, the values obtained for ATP and creatine phosphate compare favorably with 22.5 and 25.0 or 22.2 and 28.4 μmol/g dry weight in the adult rat and rabbit hearts, respectively (22,23).

We elected not to use stimulation to obtain a fixed heart rate since changes of this parameter are a manifestation of cardiac depression. In addition, we wished to identify any relationships that might exist between cardiac function, carbohydrate substrate metabolism, oxygen consumption, and high energy phosphates while the heart was depressed by these local anesthetics.

Mechanics and Oxygen Consumption

These studies have shown that, with regard to cardiac output and pressure development, bupivacaine is approximately 4.5 times as depressant as is lidocaine. Block and Covino (12) found that in the rabbit Langendorff heart preparation, 25% depression of left ventricular dP/dt required 1.38 and 16.4 mg/L for bupivacaine and lidocaine, respectively, to achieve a potency ratio of 12.

Tanz et al. (11) used the isolated guinea pig Langendorff preparation to compare the toxicities of bupivacaine and lidocaine. Their tabulated data on mechanical function and oxygen consumption indicated that 3 mg/L bupivacaine was more cardiodepressant than 30 mg/L lidocaine. At 30 min, 3.0 mg/L of bupivacaine and 30 mg/L of lidocaine yielded levels of oxygen consumption of 71.4% and 82.2% respectively, of baseline values. Our data showed a calculated 63.2% and 85.6% control for bupivacaine and lidocaine, respectively (at 15 minutes). We compared the two drugs at 15 minutes, while Tanz et al. (11) compared them at 30, 60, and 90 minutes. Thus, our protocol differed in two major respects. First, our control values differed from their comparable baseline values by approximately 2.5 times. Second, our

Table 3. Concentrations of Tissue High Energy Phosphates (μmoles/g protein) and Energy Charge

	ATP	ADP	AMP	EC
Adenine nucleotides (145)	24.6 [0.43]	7.8 [0.17]	1.8 [0.07]	0.833 [0.003]
Creatine phosphate*	No insulin (79) 23.8 [0.98]		With insulin (66) 29.3 [0.71]	

EC = (ATP + 0.5 ADP)/(ATP + ADP + AMP). Parentheses, *n*. Brackets, SEM.
*Unpaired two-tailed Student's *t* test, $P < 0.001$.

protocol would not reflect temporal changes to which their studies were sensitive. The latter impression is supported by inspection of their data showing that both oxygen consumption and coronary flow change with time, in addition to the effects of the drugs per se. At 30 minutes, hearts depressed by 3 mg/L bupivacaine had a coronary flow and myocardial oxygen consumption approximately 87% of that maintained in hearts depressed by 30 mg/L lidocaine. By 90 minutes, the difference between the two agents was more pronounced. With 3 mg/L of bupivacaine, we attained only 70% of the coronary flow and 67% of the oxygen consumption that were attained with 30 mg/L of lidocaine, compared to baseline. Thus, the difference between the drug effects was intensified by time of exposure per se. Therefore, some of the difference between our data and that of Tanz et al. (11) may be related to additional temporally related decline of cardiac performance in the presence of bupivacaine which our studies could not detect.

A difference between our results and those obtained with the Langendorff preparations may be related to the type of preparation per se. Our preparations had an oxygen consumption rate of approximately 7.7 μmol/g wwt/min compared to 2.9 μmol/g wwt/min reported by Tanz et al. (11). The difference of apparent toxicities may be related to the difference of oxygen consumption, in turn related to the work load condition at which the myocardium is functioning at the time of local anesthetic exposure.

Lynch (9) studied the contractility depressant effects of lidocaine and bupivacaine on guinea pig right ventricular trabeculae as a function of frequency of stimulation as well as concentration of local anesthetic. Both drugs, as well as etidocaine, produced the greatest depression in the rested state and the least depression at 3 Hz. Inspection of the graphically displayed data shows that at 3 Hz, 10 μM bupivacaine depressed developed tension to approximately 70% of baseline, while 40 μM lidocaine depressed developed tension to approximately 70% to 75% of control. Thus, at a frequency of 3 Hz, the bupivacaine/lidocaine molar potency ratio to depress developed tension was nearly 4:1, which is consistent with our results.

Some in vivo studies, on the other hand, have yielded different results. Nath et al. (8) studied the comparative cardiotoxic effects of the two drugs in the pig. They injected doses of anesthetic into the left anterior descending coronary artery and measured the effects on left ventricular dP/dt, aortic blood pressure, heart rate, cardiac output, and coronary venous blood flow. Using dose ranges of 0.25 to 4 mg for bupivacaine and 1 to 16 mg for lidocaine, they concluded that bupivacaine was approximately four times more depressant than lidocaine. Futhermore, Liu et al. (3) found that the bupivacaine/lidocaine accumulated lethal infusion dose in dogs was approximately 4:1. Chadwick administered bupivacaine and lidocaine to cats and, depending on the rate of administration, found the relative toxicities to be approximately 4:1.

Our studies indicate that the early (15-minute exposure) functional effects and effects on oxygen consumption actions on bupivacaine and lidocaine had a ratio close to that of their anesthetic potency, 4.59. These results agree with most in vivo studies, but differ from some of the in vitro studies. Since our data were collected at 15 minutes of influence of anesthetic, the temporal change in anesthetic effect, observed in some other studies of thirty minutes or greater, would not be present. Our data reflect short-term or acute exposure changes, which are, of course, comparable to the clinical condition.

Glucose Metabolism

In the summary of results of glucose metabolism above, the complexity of lidocaine and bupivacaine effects was apparent. If the bupivacaine potency data are equalized by multiplying the bupivacaine concentration by 4.59, it then becomes apparent that the local anesthetics behaved similarly. Furthermore, it appears that the metabolic studies showed consistently similar effects of lidocaine and bupivacaine when equivalent doses were compared, based on functional and oxygen consumption effects of the two agents. These results are, therefore, closely related to the relative anesthetic potencies of lidocaine and bupivacaine.

The major metabolic effects observed were the depressed glucose utilization and a possible net synthesis, or maintenance, of tissue glycogen as functions of local anesthetic concentration. It is of particular note that the unequivocal effect of local anesthetics, depression of glucose uptake, is a membrane effect that is a common site for their known mechanism of anesthetic activity. However, these data suggested that the local anesthetic depressant effect cannot be attributed to a decreased availability of carbohydrate for energy since there is a maintenance or net synthesis of glycogen even though perfusate glucose uptake was depressed.

High Energy Phosphates

Our results indicate that the local anesthetics have no influence on the energy charge nor creatine phosphate content. Insulin increased creatine phosphate content independently of the presence or absence of local anesthetic. Thus, the local anesthetics did not exert their depressant effects by influencing tissue high energy phosphate content.

Since our in vitro studies eliminate neurohumoral influences found in the in vivo condition, contributory effects of central nervous and autonomic response to toxic doses of drug will not be manifest. Furthermore, other variables, such as acid base changes found in the in vivo condition, will not be evident. These factors may, in part, explain the variance of our results from those that suggest a proportionately greater cardiotoxicity of bupivacaine.

Within the limitations of the crystalloid perfused, in vitro working rat heart model, we draw the following conclusions from these data:

(i) The acute depressant effects of bupivacaine and lidocaine on the cardiac functional parameters, including heart rate, mean pressure development, cardiac output, coronary flow, and myocardial oxygen consumption, are exerted in a potency ratio approximately 4.59, which is nearly anesthetic potency.

(ii) The agents exert similar depressant effects on glucose uptake at the same time that there is a maintenance or net synthesis of glycogen. Lactate production is depressed in the presence of insulin by both anesthetics and is unaffected in the absence of insulin. The two agents are indistinguishable when assessing equi-effective doses based on functional parameters and oxygen consumption, i.e., a ratio of 4.59.

(iii) Energy charge is not influenced by local anesthetic depression, nor is the influence of insulin on creatine phosphate content.

The authors wish to thank Dr. Heinrich Taegtmeyer, Division of Cardiology, for his generous provision of time and effort to review and critique these studies and offer suggestions for interpretation of the data.

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Global and Regional Myocardial Blood Flow and Metabolism during Equipotent Halothane and Isoflurane Anesthesia in Patients with Coronary Artery Disease

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KHAMBATTA HJ, SONNTAG H, LARSEN R, STEPHAN H, STONE JG, KETTLER D. Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 1988;67:936–42.

Global and regional myocardial blood flow and metabolism were examined in 20 patients with coronary artery disease before surgical stimulation. Half were anesthetized with halothane (0.8%) and half with isoflurane (1.2%). Coronary perfusion pressure decreased similarly in both groups. During halothane anesthesia coronary sinus blood flow, an index of global perfusion, decreased from an awake value of 129 ± 7 to 97 ± 7 ml/min ($P < 0.05$), and great cardiac vein blood flow, an index of regional perfusion, decreased from 60 ± 8 to 44 ± 5 ml/min ($P < 0.05$). In contrast, during isoflurane anesthesia global coronary blood flow increased from 131 ± 13 to 153 ± 16 ml/min ($P < 0.05$), while regional blood flow decreased from 68 ± 7 to 56 ± 6 ml/min ($P < 0.05$). Thus, the ratio of great cardiac vein blood flow to coronary sinus blood flow was unchanged during halothane anesthesia but decreased significantly during isoflurane. Neither global nor regional coronary vascular resistance was altered by halothane, whereas isoflurane decreased global coronary vascular resistance without affecting regional coronary vascular resistance. All patients receiving halothane had net myocardial lactate extraction. In the isoflurane group, four patients showed global lactate production and three regional lactate production. All patients demonstrating lactate production also developed electrocardiographic evidence of myocardial ischemia, which was not present before induction. The authors conclude that halothane is a preferable anesthetic to isoflurane in patients with coronary artery disease because the latter has the propensity to induce maldistribution of the coronary circulation and myocardial ischemia.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane. HEART, MYOCARDIAL BLOOD FLOW, METABOLISM.

I would rather understand one cause than be King of Persia—Democritus of Abdera (460–370 B.C.)

The primary anesthetic goal in managing patients undergoing coronary revascularization is the prevention of myocardial ischemia. Minimizing myocardial oxygen demand while maintaining adequate coronary perfusion should achieve success, but myocardial ischemia has been demonstrated to occur both randomly and as a result of hemodynamic pertubations during anesthesia in these patients (1). Perhaps the anesthetic agents themselves influence the incidence of myocardial ischemia.

Reiz et al. (2) were the first to suggest that isoflurane actually induced myocardial ischemia in patients with coronary artery disease. They postulated that both systemic hypotension and coronary steal might be responsible. In patients and animal models, many investigators have studied either isoflurance (3–7) or halothane (6,8–10) to determine the effect of anesthesia on coronary blood flow and myocardial ischemia. Yet there are no human studies of these two agents in equipotent doses prior to surgical intervention that compare global and regional coro-

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This work was supported, in part, by German Research Foundation SFB 89–Kardiologie–Göttingen. This study was done by Dr. Khambatta during his stay as Visiting Professor at the University of Göttingen.

Presented, in part, at the Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, 1986.

Received from the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York, and University of Göttingen, Göttingen, Federal Republic of Germany. Accepted for publication June 2, 1988.

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Table 1. Demographic Data of Patients Receiving Halothane Anesthesia

Patient	Age	Sex	Previous infarcts	Wall motion Abnormality	Grafts (*n*)
1	54	M	1	Yes	3
2	66	M	2	Yes	3
3	66	M	1	No	2
4	53	M	1	Yes	3
5	56	M	1	Yes	3
6	55	M	1	Yes	3
7	44	M	1	Yes	4
8	55	M	2	Yes	3
9	53	M	1	Yes	4
10	57	M	1	No	3

Table 2. Demographic Data of Patients Receiving Isoflurane Anesthesia

Patient	Age	Sex	Previous infarcts	Wall motion abnormality	Grafts (*n*)
1	54	M	2	Yes	4
2	47	M	2	Yes	4
3	74	M	1	Yes	3
4	48	M	1	Yes	3
5	45	M	1	Yes	4
6	50	M	1	Yes	3
7	62	M	2	Yes	3
8	58	M	1	Yes	2
9	63	M	0	No	2
10	54	M	1	No	2

nary blood flow and metabolism. This study was such an investigation.

Methods

Twenty patients scheduled for elective coronary artery bypass surgery were studied with their informed consent and the approval of the Institutional Review Board. All patients were receiving β-adrenergic and calcium channel blocking agents and continued to do so until surgery. Every patient had an ejection fraction greater than 0.5, and none had been in heart failure or had other significant disease. The left anterior descending coronary artery was obstructed in each case, and an average of three coronary bypass grafts were done in both groups. Additional demographic data are shown in Tables 1 and 2.

Premedication was given 2 hours before the induction of anesthesia and consisted of oral flunitrazepam 2 mg and intramuscular piritramide 15 mg and promethazine 25 mg.

In the operating room, a V5 lead of the electrocardiogram and the blood pressure tracing from a radial artery cannula were displayed continuously on an oscilloscope. A triple-lumen pulmonary artery catheter was passed through an arm vein and positioned in a pulmonary artery by continuous pressure monitoring. This catheter was used for the collection of mixed venous blood samples, intermittent recording of pulmonary artery and right atrial pressures and the determination of cardiac output by the thermodilution technique.

Under continuous pressure monitoring and fluoroscopic control, but without injecting contrast medium, a Baim coronary sinus thermodilution catheter (Elecath Corp., Rahway, NJ) (11) was advanced through the right internal jugular vein and positioned with the tip in the great cardiac vein and secured at the neck with a ligature. This catheter has two thermistors, 5 and 35 mm from the tip, so that one can simultaneously calculate thermodilution blood flows in the great cardiac vein, which drains the area perfused by the left anterior descending coronary artery (regional flow), and the coronary sinus (global flow). Room temperature normal saline, delivered by a Harvard pump at 50 $ml\cdot min^{-1}$, was used as an injectate for the Baim coronary sinus flow analyzer (Elecath Corp., Rahway, NJ) and within half a minute the thermistors in the great cardiac vein and coronary sinus achieved a steady state. Two catheter ports permit blood collection from the great cardiac vein and the coronary sinus.

The data were recorded on a 10-channel Hellige recorder (Freiburg, West Germany) and 10 minutes were required for a set of measurements at the end of each period. Paper strip recordings of the ECG and pressures were made first at a paper speed of 25 mm/sec. They were followed by recordings from the Baim coronary sinus catheter at 10 mm/sec. All ECG tracings were read at a later date by one of the investigators who was blinded to the anesthetic agent used.

Following the recordings, blood samples were collected in iced syringes simultaneously (by four individuals) from the coronary sinus, great cardiac vein, pulmonary artery, and radial artery for the determination of oxygen and lactate contents. Oxygen content was measured directly using the Lex-O_2-Con analyzer (Lexington Instruments, Lexington, MA). Blood samples for lactate were immediately deproteinized. The LDH-NAD Boehringer-Mannheim method was used. This method has been validated against the assay method described by Gutmann and Wahlefeld (12). The coefficient of variation in our laboratory was 2.9%.

Whole body oxygen consumption was calculated by multiplying (a-v) O_2 difference by cardiac output. Global and regional myocardial oxygen consumption were calculated by multiplying respective (a-v) O_2

Table 3. Systemic Hemodynamic and Metabolic Data: Awake and Half an Hour after Induction of Halothane or Isoflurane Anesthesia

	Awake	Halothane	Awake	Isoflurane
	$n = 10$		$n = 10$	
HR (beats/min)	65 ± 5	60 ± 4	69 ± 4	$83 \pm 3^{a,b}$
MAP (mm Hg)	93 ± 4	76 ± 5^{a}	100 ± 5	$65 \pm 5^{a,b}$
SBP (mm Hg)	134 ± 6	115 ± 5^{a}	142 ± 6	$87 \pm 5^{a,b}$
RPP (units)	9245 ± 380	6857 ± 125^{a}	9799 ± 510	7026 ± 312^{a}
DBP (mm Hg)	69 ± 2	58 ± 4^{a}	77 ± 5	55 ± 2^{a}
CPP (mm Hg)	62 ± 2	48 ± 2^{a}	65 ± 4	47 ± 2^{a}
PAWP (mm Hg)	10 ± 1	9 ± 1	12 ± 2	9 ± 1
RAP (mm Hg)	6 ± 0.7	5 ± 0.4	5 ± 0.7	4 ± 0.4
CI ($L \cdot min^{-1} \cdot (m^2)^{-1}$)	3.1 ± 0.1	2.4 ± 0.1^{a}	3.2 ± 0.1	2.7 ± 0.1^{a}
SVR (units)	28 ± 1	30 ± 1	30 ± 1	$25 \pm 2^{a,b}$
$\dot{V}O_2$ ($ml \cdot min^{-1} (m^2)^{-1}$)	123 ± 7	95 ± 6^{a}	107 ± 5^{c}	75 ± 6^{a}
$PaCO_2$ (mm Hg)	43 ± 2	39 ± 1	42 ± 2	39 ± 1

Values represent mean ± SE. HR, heart rate; MAP, Mean arterial pressure; RPP, Rate pressure product; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CPP, Coronary perfusion pressure; PAWP, Pulmonary artery wedge pressure; RAP, Right atrial pressure; CI, Cardiac index, SVR, Systemic vascular resistance; $\dot{V}O_2$, Whole body oxygen consumption; and $PaCO_2$, Arterial carbon dioxide tension.

[a] $P < 0.05$: Awake compared to anesthetized values in each group.

[b] $P < 0.05$: The change from awake to anesthetized values in halothane group compared to a similar change in isoflurane group.

[c] $P < 0.05$: Awake values in halothane group compared to those in isoflurane group.

differences by the corresponding flows. Global and regional lactate extraction were determined in $mmol \cdot 1^{-1} \cdot min^{-1}$ by multiplying the respective (a-v) lactate differences in mmol/L with the corresponding coronary flows in ml/min. Coronary perfusion pressure was obtained by subtracting pulmonary artery wedge pressure from diastolic blood pressure. Global and regional coronary vascular resistances were determined by dividing mean diastolic blood pressure minus pulmonary artery wedge pressure (PAWP) by the respective coronary blood flows. Mean diastolic blood pressure was defined as diastolic blood pressure + 1/7 (systolic minus diastolic blood pressure). Systemic vascular resistance was calculated by dividing (mean arterial pressure minus right arterial pressure) by cardiac output.

The first set of measurements was made in the awake state breathing room air and the second set half an hour after the induction of anesthesia but before surgical stimulation. Anesthesia was introduced with etomidate 20 mg IV. Muscle relaxation was achieved with pancuronium 0.2 mg/kg and the trachea then was intubated. Ventilation was controlled to maintain $PaCO_2$ at 40 mmHg. Ambient temperature was controlled to maintain the patients at 37°C. Patients were randomized and received either halothane or isoflurane in a gas mixture of equal volumes of oxygen and air. The end expired anesthetic concentrations were measured at the proximal end of the endotracheal tube by an infrared analyzer, Normac (Datex, Helsinki, Finland), and maintained at 0.8% for halothane and 1.2% for isoflurane. These values represent concentrations of approximately 1 MAC. When the study was completed, additional anesthetics were administered and the surgery proceeded.

Within each group all statistical comparisons were done by paired Student's *t*-test. When the two groups were compared, an unpaired two-tailed Student's *t*-test was used. $P < 0.05$ was considered significant.

Results

The systemic hemodynamic and metabolic data in the two groups are listed in Table 3. The heart rate was not significantly changed in patients receiving halothane, but increased 20 percent in those given isoflurane. Mean arterial pressure decreased significantly in both groups, but the decrease in the isoflurane group was larger. Systolic and diastolic blood pressures also decreased significantly in both groups, and the decrease in systolic pressure of the isoflurane group was greater than that of the halothane group. During anesthesia the two groups had similar diastolic blood pressures and coronary perfusion pressures. After induction systemic vascular resistance was unchanged in the halothane group but decreased significantly in patients given isoflurane. Cardiac index and whole body oxygen consumption both decreased during anesthesia, but the change was the same in the two groups.

The coronary hemodynamic and the myocardial metabolic data in the two groups are given in Table 4. There was no change in either global or regional vascular resistance in the patients anesthetized with

Table 4. Myocardial Hemodynamic and Metabolic Data: Awake and Half an Hour after Induction of Halothane or Isoflurane Anesthesia

	Awake	Halothane	Awake	Isoflurane
	$n = 10$		$n = 10$	
CSBF (ml/min)	129 ± 7	97 ± 7[a]	131 ± 13	153 ± 16[a,b]
GCVBF (ml/min)	60 ± 8	44 ± 5[a]	68 ± 7	56 ± 6[a]
GCVBF/CSBF	0.47 ± 0.03	0.45 ± 0.03	0.52 ± 0.04	0.37 ± 0.03[a,b]
CSO_2 (ml/vol%)	8.2 ± 0.1	9.2 ± 0.1[a]	7.6 ± 0.1[c]	11.0 ± 0.1[a]
$GCVO_2$ (ml/vol%)	5.7 ± 0.1	6.7 ± 0.1[a]	5.7 ± 0.1	7.5 ± 0.1[a]
$GS\dot{V}O_2$ (ml/min)	12 ± 1	9 ± 1[a]	11 ± 1	8 ± 1[a]
$GCV\dot{V}O_2$ (ml/min)	7 ± 1	5 ± 0.4[a]	8 ± 0.4	5 ± 0.4[a]
CSLE ($mmol{\cdot}L^{-1}{\cdot}min^{-1}$)	6 ± 2	11 ± 3[a]	10 ± 3	4 ± 4[b]
GCVLE ($mmol{\cdot}L^{-1}{\cdot}min^{-1}$)	4 ± 1	5 ± 2	6 ± 1	0.1 ± 4[a,b]
CSVR (units)	0.54 ± 0.04	0.62 ± 0.04	0.61 ± 0.06	0.36 ± 0.02[a,b]
GCVVR (units)	1.29 ± 0.16	1.42 ± 0.09	1.16 ± 0.12	1.00 ± 0.1

Values represent mean ± SE. CSBF, Coronary sinus blood flow—global myocardial blood flow; GCVBF, Great cardiac vein blood flow—regional myocardial blood flow; CSO_2, Coronary sinus oxygen content; $GCVO_2$, Great cardiac vein oxygen content; $CS\dot{V}O_2$, Global myocardial oxygen consumption; $GCV\dot{V}O_2$, Regional myocardial oxygen consumption; CSLE, Coronary sinus—global myocardial lactate extraction; GCVLE, Great cardiac vein—regional myocardial lactate extraction; GSVR, Global myocardial coronary vascular resistance; and GCVVR, Regional myocardial coronary vascular resistance.

[a] $P < 0.05$: Awake compared to anesthetized values in each group; no significant change between the two awake groups.

[b] $P < 0.05$: The change from awake to anesthetized values in halothane group compared to a similar change in isoflurane group.

[c] $P < 0.05$: Awake values in halothane group compared to those in isoflurane group.

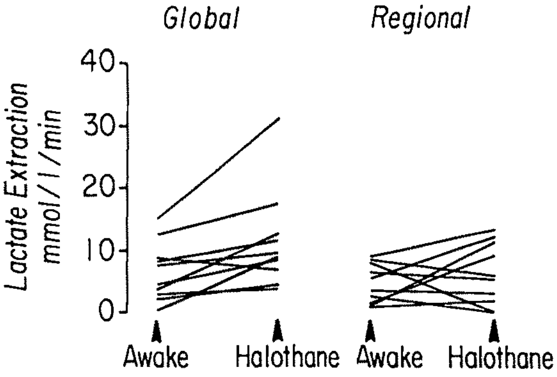

Figure 1. Global and regional lactate extraction during halothane anesthesia in individual patients.

halothane. Isoflurane, on the other hand, caused a 41% decrease in global vascular resistance without a change in regional vascular resistance. As a result, coronary sinus blood flow decreased 25% in patients receiving halothane and increased 17% in patients given isoflurane. Great cardiac vein blood flow decreased in both groups. The ratio of regional to global perfusion was unchanged in those receiving halothane, but decreased significantly, from 0.52 ± 0.04 to 0.37 ± 0.03, in those receiving isoflurane. Global and regional myocardial oxygen consumption decreased with both anesthetics. All of the patients anesthetized with halothane developed global and regional net lactate extraction (Fig. 1); however, four patients given isoflurane had global lactate production and three regional lactate production (Fig. 2). There were no changes in the S-T segments of the ECG in any of the patients given halothane. Patients 1, 3, 6, and 8 of the isoflurane group developed new ischemic ECG patterns as well as lactate production.

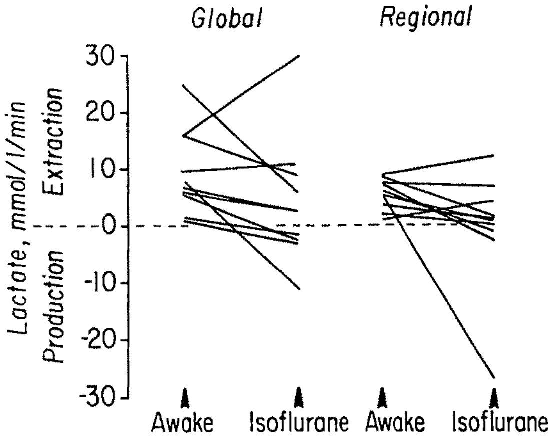

Figure 2. Global and regional lactate extraction or production during isoflurane anesthesia in individual patients.

Data from the four patients who developed ischemia with isoflurane anesthesia are detailed in Table 5. The ischemic patients did not have more rapid heart rates than the nonischemic patients. Moreover, the patient who had the fastest heart rate (No. 8) had one of the lowest values of lactate production. Mean arterial pressure and coronary perfusion pressure in this subgroup were no different from the isoflurane group as a whole. Neither global nor regional myocardial blood flow in patients with myocardial ischemia was statistically different from blood flows in the group as a whole.

Table 5. Relevant Hemodynamic and Metabolic Data in Individual Patients Who Developed Ischemic Changes under Isoflurane Anesthesia

Patient	1	3	6	8	Mean	Status
HR (beats/min)	65	67	98	70	75	A
	74	72	97	100	86	I
MAP (mmHg)	96	115	105	90	102	A
	61	61	61	69	63	I
CPP (mmHg)	56	53	57	60	57	A
	42	42	47	45	44	I
CSBF (ml/min)	101	129	141	91	116	A
	109	150	160	115	134	I
GCVBF (ml/min)	55	83	75	66	70	A
	38	60	60	53	53	I
GCVBF/CSBF	0.54	0.64	0.53	0.72	0.61	A
	0.35	0.40	0.38	0.46	0.40	I
CSO_2 (vol%)	7.2	5.6	10.1	5.6	7.1	A
	8.6	6.5	15.5	8.5	9.8	I
$GCVO_2$ (vol%)	5.4	4.6	7.2	5.0	5.6	A
	5.5	6.1	9.3	7.5	7.1	I
CSLE ($mmol \cdot L^{-1} \cdot min^{-1}$)	8.1	1.3	1.4	5.5	4.1	A
	−10.9	−2.7	−2.0	−2.3	−4.5	I
GCVLE ($mmol \cdot L^{-1} \cdot min^{-1}$)	5.5	5.8	6.8	6.1	6.1	A
	−26.6	−1.0	−2.1	0	−7.4	I
CSVR (units)	0.66	0.53	0.53	0.76	0.62	A
	0.43	0.35	0.36	0.49	0.39	I
GCVVR (units)	1.22	0.82	1.19	0.92	1.03	A
	1.24	0.62	0.73	0.70	0.82	I

A = awake; I = isoflurane anesthesia.

Discussion

Both halothane (13–16) and isoflurane (2,3,17,18) cause dose-related myocardial depression, the degree of depression being a function of the depth of anesthesia (4,15,16,18,19). In this study, significant decreases were observed in both cardiac index and mean arterial pressure. The decrease in cardiac index was not significantly different in the two groups. Compared to halothane, patients given isoflurane sustained greater decreases in both mean arterial and systolic arterial pressures, but diastolic pressures in the two groups were not significantly different. It is the diastolic pressure that most affects coronary perfusion, and the coronary perfusion pressures were identical in both groups during anesthesia. Thus, it is unlikely that the observed differences in arterial pressure between the two groups caused the supply of myocardial oxygen to be different.

No clinically available irreproachable method for measuring global and regional coronary blood flow exists today. The thermodilution technique has been used for over 10 years and has been validated in patients undergoing surgery for coronary artery disease (20), but the method has its limitations (21,22). Surgical manipulation can alter catheter position. Small changes in thermistor position affect reproducibility; however, once our catheters were placed and the proximal ends secured, patient movement was kept to a minimum, and the clear pressure tracing from the tip indicated that the tip was not wedged.

The left anterior descending coronary artery perfuses 50–70% of the human left ventricular mass under resting conditions (23). The ratio of great cardiac vein blood flow to coronary sinus blood flow reflects that distribution. The measured ratio in both our groups in the awake state was 0.5 and is consistent with previous reports (3,23).

In the halothane group there were 25% decreases in both global and regional myocardial blood flow and oxygen consumption with the induction of anesthesia. Others have also observed parallel changes in global coronary blood flow and oxygen consumption (13,17). In one study the authors were not able to demonstrate a relationship between coronary blood flow and oxygen consumption during halothane anesthesia, but 3% halothane was used (10).

In our isoflurane group, the parallel relationship between coronary blood flow and myocardial oxygen consumption was not observed. Though global and regional myocardial oxygen consumption both decreased, there was an associated increase in global blood flow and a decrease in regional blood flow. The ratio of regional to global coronary blood flow therefore decreased.

We observed no changes in either systemic vascular resistance or global and regional coronary vascular resistances during halothane administration. Though regional coronary vascular resistance was not measured, Reiz et al. (15) observed no change in global coronary vascular resistance. However, they noted a decrease in systemic vascular resistance during halothane anesthesia, which may have been because their patients experienced large decreases in arterial pressure. In the present study, halothane caused neither systemic nor coronary vasodilation, and thus the relationship between global and regional coronary blood flow and between myocardial blood flow and oxygen consumption were well maintained. On the other hand, global coronary vascular resistance decreased 41% with the induction of isoflurane anesthesia, while regional coronary vascular resistance was unchanged. Direct measurement of coronary vascular resistance is not possible in a clinical study; hence, it is calculated. Marcus (24) has detailed ten different ways for computing coronary vascular resistance. However, he states that when a perturbation produces a modest change in coronary vascular resistance (±15 percent), the magnitude and direction of the change may depend on the method employed to compute coronary vascular resistance, but when a given intervention produces a major (±50 percent) change in coronary vasomotor tone, the effect will be apparent regardless of the formula employed (24). Thus, the 41% reduction in global coronary vascular resistance noted by us during isoflurane anesthesia constitutes a definitive change independent of the computing methodology.

The relationship between coronary vascular resistance and coronary flow during anesthesia appears to vary. In one study of isoflurane in which systolic blood pressure was lowered to a predetermined level by adjusting the inspiratory concentration of isoflurane, global coronary vascular resistance decreased but blood flow did not change (18). In another report, 0.4% isoflurane was administered for 20 minutes and an 18% decrease in global coronary blood flow occurred without a change in coronary vascular resistance (25). When 0.7–1.3% isoflurane was administered to treat the hypertensive stress response following sternotomy, there was no change in global or regional coronary blood flow (26). In another study of isoflurane at 1.5 MAC in the presence of 40% nitrous oxide, the authors found no increase in global coronary blood flow but a decrease in regional flow, as well as decreases in both global (40%) and regional (22%) coronary vascular resistance (27). The differences in these studies, we believe, are due to differences in protocol. In this study we chose to compare clinically relevent doses of the two anesthetics before surgical stress.

Under normal conditions, the heart uses lactate a a substrate and there is lactate extraction in th myocardium. Myocardial lactate production implie myocardial ischemia (28). Lactate produced in a ischemic area and diluted with blood from nonischemic areas might well cause the mixed blood to sho diminished lactate extraction rather than productio (28). In all our patients who received 1 MAC halothane, a net lactate extraction occurred. In contrast there was a 60% reduction in lactate extraction globally and a 600% reduction in lactate extraction regionally in patients receiving 1 MAC isoflurane Moreover, global lactate production occurred in fou of the isoflurane patients and regional lactate production in three. Lactate production during isofluran anesthesia has been reported before (2,3,18), but th mechanism responsible for it remains obscure.

A change in heart rate alters myocardial oxyge demand. In patients receiving isoflurane, there was significant increase in heart rate, but both global an regional myocardial consumption decreased. Othe factors that influence myocardial oxygen demand ar myocardial contractility, preload, and afterload. Myocardial contractility was not measured, but isofluran is a negative inotrope. The preload was not altered but the afterload decreased significantly. Thus, tw of the four determinants of myocardial oxygen demand decreased during isoflurane anesthesia an only one increased. Moreover, there was no statistica correlation between myocardial lactate productio and heart rate. Patient No. 8, who had the highes heart rate, had one of the lowest values of lactat production.

It may be argued that controlling blood pressur and heart rate during a study removes two of th variables responsible for inducing ischemia. However, if heart rate and blood pressure are manipulate by pharmacological intervention, then the agent used may themselves affect coronary blood flow While possible in animal experiments, these drug induced manipulations are hard to justify in humans and man is the species in which coronary arter disease exists.

We have demonstrated that 1 MAC isofluran anesthesia produced global coronary vasodilation, a evidenced by a decrease in global coronary vascula resistance and an increase in global coronary bloo flow. At the same time, regional coronary blood flo decreases and regional coronary vascular resistanc remains unchanged, probably because the stenoti coronary vasculature is unable to dilate. Hence, ther is a diversion of blood from ischemic to nonischemi areas of the heart. We believe that this coronar maldistribution—coronary steal—is responsible fo the ischemic changes in patients receiving 1 MAC isoflurane. Halothane in an equipotent concentration caused no coronary maldistribution. Therefore, at these concentrations isoflurane may be inadvisable for patients with coronary artery disease.

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ANESTH ANALG
1988;67:943–8

Local Anesthetics Potentiate Spinal Morphine Antinociception

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Some investigators have postulated a synergistic analgesic effect of local anesthetic agents and opiates when given intrathecally or epidurally, but little objective evidence has been presented to quantitate such an effect. A study was therefore undertaken to compare in mice the antinociceptive effects of intrathecal injections of mixtures of morphine with bupivacaine or lidocaine with the effects of these agents when administered alone. The antinociceptive effects (tail-flick and hotp-late tests) of morphine (0.1–1.6 μg) with either bupivacaine, 25 μg, or lidocaine, 200 μg, were significantly greater than the effects of morphine or the local anesthetics when administered alone. When morphine was administered with the local anesthetics, the intensity and the duration of antinociception were greater, although the time courses of the effects resembled that of morphine administered alone. An enhanced effect was also observed when combinations of local anesthetics and low doses of morphine were used that by themselves had no or little effect. The addition of morphine did not affect the motor block produced by the local anesthetics. The results indicate a potentiating effect of local anesthetics on spinal morphine antinociception, a finding that may have important clinical implications.

Key Words: INTERACTIONS, DRUG—local anesthetics, morphine. ANESTHETIC TECHNIQUES—spinal. ANALGESICS—morphine, spinal.

Intrathecal and epidural administration of low doses of morphine and related agents has become increasingly common in the management of pain. The analgesia resulting from the administration of these agents is most likely a result of activation of spinally located opiate receptors. The use of opiates in conjunction with spinal or epidural local anesthesia to afford prolonged postoperative pain relief has been the subject of several studies. For example, intrathecally injected mixtures of morphine with tetracaine or bupivacaine produced excellent postoperative pain relief of significantly longer duration than the local anesthetics alone without affecting the parameters of surgical anesthesia (1–3). Similar results have been reported after epidural injection of bupivacaine together with morphine (4–7). In addition, combinations of morphine and a local anesthetic such as bupivacaine at concentrations that do not produce motor blockade may offer advantages for the control of labor and cancer pain (8–10).

Some investigators have postulated a synergistic analgesic effect of local anesthetic agents and opiates when given intrathecally or epidurally as combinations but little objective experimental evidence has been presented to quantitate such an effect (6,10). Concomitant use of local anesthetics and opiates appears, however, to have a considerable potential for the management of pain with spinal and epidural anesthesia. A possible synergistic analgesic effect between local anesthetics and opioids may have important clinical implications, but this effect is difficult to evaluate experimentally in man. The present study in mice was undertaken to compare the antinociceptive effects of combinations of intrathecal morphine and bupivacaine or lidocaine with the effect of each of these agents administered intrathecally by themselves.

Materials and Methods

Animals

Male mice of the NMRI strain, weighing 20–24 g, (Anticimex, Sweden) were used. Before the experiment they were housed on sawdust bedding material, in groups of ten animals, for at least one week in animal rooms thermostatically maintained at 21 ± 1°C with a 12 hours on, 12 hours off lighting schedule

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Received from the Research and Development Laboratories, Astra Alab AB, Södertälje, Sweden. Accepted for publication April 28, 1988.

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(light on at 6:00 AM). The experiments were performed between 8:00 AM and 4:00 PM. The study was approved by the Committee for Ethical Issues of the Swedish Board of Agriculture.

Test Procedure

All agents were administered into the subarachnoid space by lumbar puncture (11). In brief, a 30-gauge stainless steel cannula was inserted through the L4–5 vertebral interspace. The test solution was delivered in a volume of 5 μl with a Hamilton microsyringe attached to the cannula by a PE50 polyethylene tube. Each solution was injected in groups of six mice. Different animals were used in each group.

The animals were tested for tail-flick (12) and hot-plate (13) reaction latencies before the acute injection and at the times indicated in the figures. The tail-flick test was conducted with an IITC Inc. (Landing, NJ) Model 33 analgesia meter. The rheostat-controlled light beam was focused on the tip of the tail, and the time interval from the onset of the heat stimulus to the flick of the tail was recorded. A cutoff time of 10 seconds was used. Hot-plate testing was performed with an IITC Inc. Model 35D Analgesia Meter with the surface temperature of the plate set to 58 ± 2°C. Pain response latency was determined before and after intrathecal injection by recording the time at which the animal responded by licking or vigorous shaking of a paw or by jumping. The animals were removed from the plate if they did not respond to the heat within 30 seconds. The motor blockade was assessed each time antinociception was tested. The duration of motor blockade was the time between onset of loss of weight support and return of the animal's ability to walk properly.

Test Solutions

Morphine (ACO Pharmaceuticals, Sweden), bupivacaine, and lidocaine (Astra Alab, Sweden) were used in the form of their hydrochloride salts and were dissolved in 0.9% sterile saline. The concentrations of morphine used were obtained by dilution of a stock solution on the day of the experiment. Bupivacaine and lidocaine were used as 0.5% and 4.0% solutions respectively. The pH of the solutions ranged between 6.0–6.6. The injections were performed with coded solutions, so that the experimenter was not aware of the treatment being administered.

The antinociceptive effect was calculated by transforming response latencies to the maximal possible effect (MPE%):

$$\text{MPE\%} = 100 \times \frac{\text{Test Latency} - \text{Baseline Latency}}{\text{Cut-Off Time} - \text{Baseline Latency}}$$

Statistics

The statistical comparisons were made using the variance analysis for two groups (Mann–Whitney test, unpaired samples) at 5, 10, 15, 30, 45, 60, 75, 90, 105, and 120 minutes after injection. A difference was considered as statistically significant at $P \leq 0.05$.

Results

Injection of the vehicle (0.9% saline) in a group of six mice produced no consistent changes in the tail-flick or hot-plate response latencies. Maximum tail-flick response latency was 5.6 ± 0.4 seconds ($\bar{X}$ ± SEM) observed 10 minutes after the injection. The corresponding response latency under baseline conditions was 5.1 ± 0.2 seconds. Maximum hot-plate response latency was 7.3 ± 0.6 seconds (30 minutes after injection) compared with a pre-drug latency of 5.8 ± 0.7 seconds. Injection of saline did not affect motor function.

Motor Blockade

Bupivacaine, 25 μg, and lidocaine, 200 μg, gave rise to motor blockade of the hind legs. None of the morphine doses employed produced any evidence of motor impairment, and there was no evidence that the duration of motor block induced by bupivacaine or lidocaine was prolonged by the addition of morphine. For example, the duration of block with the mixture of bupivacaine with 1.6 μg morphine was 10.3 ± 1.3 minutes ($\bar{X}$ ± SEM, $n = 6$) compared with 8.0 ± 0.9 minutes for bupivacaine alone. The motor blockade produced by lidocaine together with 0.4 μg morphine lasted 8.7 ± 1.2 minutes compared with 10.1 ± 0.5 minutes for lidocaine alone.

Tail-Flick Test

When morphine alone was injected intrathecally, a dose of 0.1 μg gave a comparatively weak and short-lasting antinociception with a peak effect ten minutes after injection (Fig. 1A). The intensity and duration of the antinociceptive effect increased in a dose-dependent manner after 0.4, 0.8, and 1.6 μg morphine. Two hours after injection of 1.6 μg morphine, the tail-flick response was still blocked to about 75% of the maximum effect.

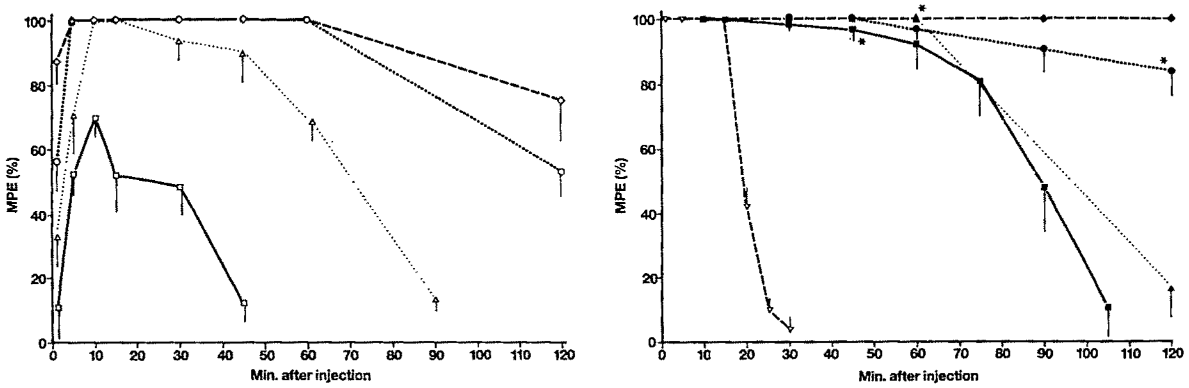

Figure 1. Tail-flick test in the mouse. Antinociceptive effect (MPE% ± SEM, $n = 6$) after intrathecal injection of: (A) morphine at doses of 0.1 μg (□), 0.4 μg (△), 0.8 μg (○), and 1.6 μg (◇). (B) the same doses of morphine (filled symbols) together with 25 μg bupivacaine. ∇ = 25 μg bupivacaine alone. * Indicates the last common measure point at which the difference between the mixture and morphine alone (A) was statistically significant ($P \leq 0.05$).

A dose of 25 μg bupivacaine blocked the tail-flick response with a rapid onset (Fig. 1B). The maximum effect lasted for about 15 minutes, after which the response latency rapidly declined to baseline values. When morphine was injected together with bupivacaine, the antinociceptive effect was significantly greater than when the two agents were given separately (Fig. 1B). A mixture of 0.1 μg morphine and 25 μg bupivacaine blocked the tail-flick significantly longer than did bupivacaine alone. The response latency returned to baseline values after almost two hours, whereas the corresponding times were approximately 30 minutes for bupivacaine alone and 45 minutes for morphine alone. An enhanced antinociceptive effect was also seen after mixing higher doses of morphine with bupivacaine, although the time for return to normal responsiveness was not determined.

Lidocaine, 200 μg, blocked the tail-flick response to radiant heat almost instantaneously, and recovery from block was rapid (Fig. 2). A dose of 0.4 μg morphine showed a slower onset of block and a slower recovery. When lidocaine and morphine were combined the injected solution resulted in tail-flick block significantly more rapid in onset with significantly longer duration than with morphine or lidocaine alone.

Hot-Plate Test

In contrast to the tail-flick test, 0.1–0.4 μg morphine intrathecally did not increase the hot-plate response latency. A dose of 0.8 μg morphine had an antinociceptive effect that was further improved by increasing the dose to 1.6 μg (Fig. 3A).

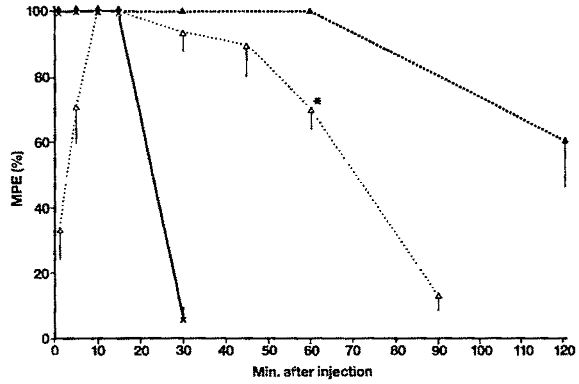

Figure 2. Tail-flick test in the mouse. Antinociceptive effect (MPE% ± SEM, $n = 6$) after intrathecal injection of 200 μg lidocaine (x), 0.4 μg morphine (△), and a mixture of 200 μg lidocaine and 0.4 μg morphine (▲). * Denotes statistically significant difference ($P \leq 0.05$) between morphine alone and morphine plus lidocaine.

Bupivacaine, 25 μg, produced complete motor blockade of the hind legs that was of a short duration and normal responsiveness to hot-plate stimulus returned soon after return of motor function (Fig. 3B). The degree and duration of the antinociceptive effect were significantly greater after injection of the combination of morphine and bupivacaine than they were when the two agents were given alone (Fig. 3B). Synergism was present even with low doses (0.1 and 0.4 μg) of morphine. When these doses were injected without bupivacaine they had no effect. Similarly, the mixture of 200 μg lidocaine and 0.4 μg morphine extended the period of increased hot-plate response latency significantly beyond the duration of effect seen with lidocaine alone. The same dose of morphine without lidocaine was devoid of any effect (Fig. 4). As with bupivacaine, recovery from block of hot-plate response with lidocaine was closely associated with return normal motor function.

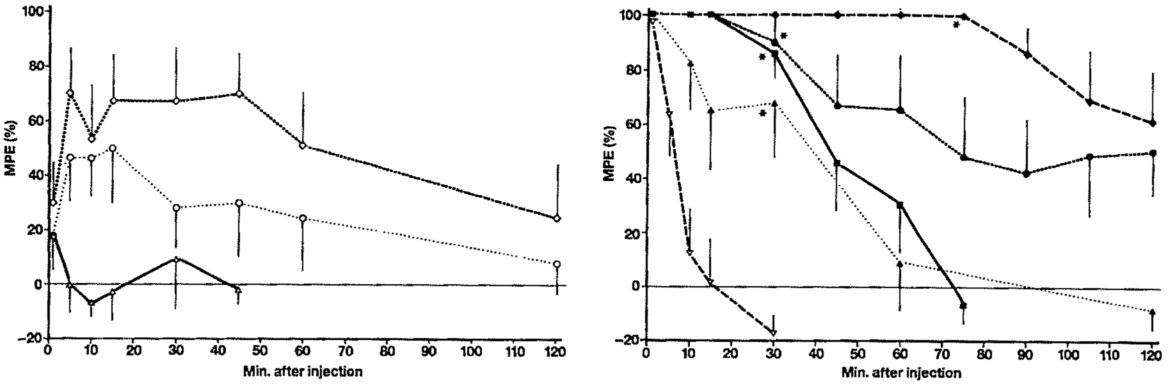

Figure 3. Hot plate test in the mouse. Antinociceptive effect (MPE% ± SEM, $n = 6$) after intrathecal injection of: (A) 0.4 μg morphine (△), 0.8 μg (○), and 1.6 μg (◇). (B) 0.1 μg morphine (□), and the same doses of morphine as in (A) (filled symbols) mixed with 25 μg bupivacaine. ▽ = bupivacaine alone. *Denotes statistically significant differences between the mixtures and morphine alone (A) ($P \leq 0.05$). See also Figure 1.

Discussion

The results of this study indicate that, upon subarachnoid injection, the antinociceptive effects of morphine when combined with bupivacaine or lidocaine were significantly greater than when morphine or either of the two local anesthetics was injected alone. A significantly enhanced effect was obtained even when mixtures were injected that contained doses of morphine so low that by themselves they had little or no effect. Both the degree and the duration of antinociception were improved, the time courses of the recorded effects resembling those after morphine injected separately. Addition of morphine did not affect the motor blockade produced by the local anesthetics. Thus, our results demonstrate a synergism between morphine and local anesthetics with regard to antinociception, results supporting clinical observations on analgesic efficacy of the combination of local anesthetics and opioids during spinal or epidural anesthesia (6,10). In addition, our findings indicate that the antinociceptive action of morphine is potentiated by the simultaneous administration of the local anesthetics.

Local anesthetics and morphine differ significantly with regard to physicochemical properties essential for the transfer of the agents to the neural targets. Principal differences exist also with respect to sites, mode, and mechanism of action. With local anesthetics, the base form penetrates tissue barriers with relative ease due to its lipophilic character. The obstacles to diffusion are comparatively few after intrathecal injection as evidenced, for example, by the rapid onset of effects in the present study. In contrast, the rather long latency period before an antinociceptive effect was observed with morphine reflects slow penetration to the sites of action due to the hydrophilic character of the molecule.

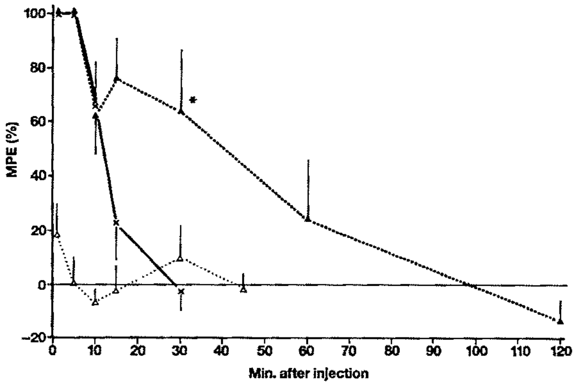

Figure 4. Hot plate test in the mouse. Antinociceptive effect (MPE% ± SEM, $n = 6$) after intrathecal injection of 200 μg lidocaine (x), 0.4 μg morphine (△), and 200 μg lidocaine plus 0.4 μg morphine (▲). *$P \leq 0.05$ for mixture vs morphine alone.

Most evidence points to the spinal roots as the main targets for subarachnoid conduction block by local anesthetics, although a depressant action on the nervous transmission in the cord cannot be excluded. The antinociceptive effect of morphine is considered to take place through interaction with specific receptors, especially those of the μ-type located primarily in the superficial Rexed laminae of the dorsal horn (14) but also in the dorsal roots (15). Morphine thus seems to have both postsynaptic and presynaptic binding sites.

It has been convincingly shown that local anesthetics block both propagation of the neural action potential, as well as generation of an action potential, by a selective effect on sodium channels that prevents the depolarization of the nerve membrane. The main electrophysiological action of an opiate such as morphine is proposed to be hyperpolarization of the nerve cell membrane due to opening of potassium channels (16,17). This can lead to reduction in release of putative transmitter either by conduction block or by reduction of calcium currents during the action potential that promote transmitter release. Hyperpolarization of the membrane also reduces cell firing postsynaptically. Evidence exists, then, that local anesthetics and morphine differ in their electrophysiological actions in that the former closes sodium channels whereas the latter acts by opening potassium channels. The precise mechanisms behind a potentiating effect of local anesthetics on the antinociceptive effect of morphine at the membrane level remain to be demonstrated.

The hypothesis that at least one part of the spinal effect of morphine might be the result of the block of action potential propagation through the same mechanism as local anesthetics is not supported by studies on peripheral nerves. Some depression of action potentials by opioid in nerve fibers of different types has been found. The effects, however, are inconsistent, even with preparations having few barriers to diffusion, with high concentrations of opioids, and with long exposure times (18–20). Furthermore, morphine has little affinity for binding to a sodium channel site associated with local anesthetic action (21). One study suggests competitive inhibition of opiate binding by local anesthetics (22). Recent results indicate, however, that, even if local anesthetics bind to opiate receptors, the affinity is very low (Ask, personal communication).

Bupivacaine has been reported to decrease the spinal cord blood flow (23) although lidocaine has no such effect (24). Therefore, delayed absorption of morphine due to a vasoconstrictive effect of local anesthetics does not explain the augmented antinociception observed in the present study of mixtures of opioids and local anesthetics because an enhanced effect was seen with both bupivacaine and lidocaine. Nor is it likely that morphine should have significantly affected the rate of absorption of the local anesthetics from the spinal cord and roots. Although morphine decreases spinal cord blood flow (25), the concomitant use of morphine and local anesthetics did not prolong the motor block induced by the local anesthetics in this study.

In conclusion, our results demonstrate a synergistic antinociceptive effect of intrathecal morphine and local anesthetics. Because the combined effect of the two types of drugs was stronger than their individual effects (but with a time course resembling that after morphine alone), the findings indicate that the local anesthetics potentiated morphine antinociception.

Care must be taken in extrapolation of the present results to man. In a clinical situation in which the combination of a local anesthetic and morphine epidurally or intrathecally is indicated it may be possible to afford satisfactory analgesia with a comparatively low dose of morphine. Whether the dose of a local anesthetic in a combination with morphine can also be reduced in situations in which motor impairment is undesirable remains to be studied. Any reduction in doses will decrease the likelihood of side effects from both types of agents. Combinations of morphine and local anesthetics may also provide means to maintain pain relief while avoiding problems associated with tachyphylaxis after continuous epidural administration of, for example, bupivacaine (26).

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1988;67:949–55

Left Ventricular Function during Propofol and Fentanyl Anesthesia in Patients with Coronary Artery Disease: Assessment with a Radionuclide Approach

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LEPAGE J-YM, PINAUD ML, HELIAS JH, JUGE CM, COZIAN AY, FARINOTTI R, SOURON RJ. Left ventricular function during anesthesia in patients with coronary artery disease: assessment with a radionuclide approach. Anesth Analg 1988;67:949–55.

Using gated radionuclide ventriculography and invasive cardiac monitoring, the effects of propofol alone and in combination with fentanyl on left ventricular (LV) volumes and function were investigated in 10 ASA III, unpremedicated patients (51–75 years) with coronary artery disease (NYHA II–III). Anesthesia was induced with propofol (2 mg/kg) followed by an infusion (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Vecuronium (0.05 mg/kg) was administered and ventilation (FI_{O_2}, 1.0) was manually controlled via a face mask (FE_{CO_2}, 4–5%). Data acquisitions were serially obtained over 15 minutes after the bolus IV injection of propofol and 5 minutes after the injection of fentanyl (5 μg/kg). Propofol induced a rapid decrease (15%) in mean arterial pressure (MAP) exclusively related to a decrease in cardiac index (CI), without reduction in indexed systemic vascular resistances (SVRI). Despite the decrease in MAP, heart rate did not change. The decrease in CI was associated with a lower preload. After the addition of fentanyl, MAP decreased significantly (35%) below the last set of propofol measurements. The decrease in MAP was associated with a reduction in CI and SVRI. Fentanyl was also associated with a significant decrease in heart rate (16%) resulting in a decrease in CI, whereas stroke index and end diastolic volume did not change. Neither global ejection fraction (EF) nor end systolic volume changed significantly at any time, nor were there changes in the ECG or in regional ejection fractions (REF). The absence of changes in REF was consistent with lack of wall motion abnormalities of the left ventricle. Propofol alone and in combination with fentanyl does not alter LV performance in patients with good LV function. However, the magnitude of MAP reduction might jeopardize coronary perfusion in severe ischemic heart disease.

Key Words: ANALGESICS—fentanyl. ANESTHETICS, INTRAVENOUS—propofol. HEART—myocardial function, anesthetics. MEASUREMENT TECHNIQUES—cardiac output, radioactive tracers.

The efficacy and usefulness of propofol in combination with fentanyl have been demonstrated in patients with good LV function undergoing coronary artery bypass surgery (1). Propofol–fentanyl anesthesia is capable of blocking autonomic sympathetic responses to noxious stimuli (2). However, Williams et al. (3) reported that there is potential for hemody-

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This work was supported in part by the University of Nantes Institutional Grants Program.

Presented in part at the annual meeting of the International Anesthesia Research Society, San Diego 1988.

Received from the Département d'Anesthésie–Réanimation Chirurgicale et Service de Médecine Nucléaire, Hotel-Dieu, Centre Hospitalier Universitaire, Nantes, France, and the Service Pharmaceutique, Centre Hospitalier Universitaire Xavier Bichat, Paris, France. Accepted for publication May 9, 1988.

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Abbreviations: LV, left ventricular; MAP, mean arterial pressure; RAP, right atrial pressure; PAP, pulmonary artery pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; thCO, thermodilution cardiac output; thCI, thermodilution cardiac index; SV, stroke volume; SI, stroke index; thSI, thermodilution stroke index; SVR, systemic vascular resistances; SVRI, indexed systemic vascular resistances; CaO2, arterial oxygen content; $C\bar{v}_{O2}$, mixed venous oxygen content; $a-\bar{v}_{O_2}$, arteriovenous difference in oxygen contents; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_2I$, indexed oxygen consumption; OER, oxygen extraction ratio; Tc, technetium; isCO, isotopic dilution cardiac output; deCO, densitometric cardiac output; AF, attenuation factor; ED, end diastolic; ES, end systolic; ESV, end systolic volume; EDV, end diastolic volume; EF, global ejection fraction; REF, regional ejection fraction.

namic depression when propofol is used in combination with fentanyl, especially in patients with limited cardiovascular reserve. The net effect on hemodynamics of the addition of the fentanyl negative chronotropic effect (4) and the frequent absence of increased heart rate after propofol administration (5,6) must be questioned. Radionuclide cineangiography effectively reproduces results obtained with contrast angiography in the assessment of LV volumes and function and provides a complementary tool for assessment of cardiac performance during anesthesia (7,8). Using gated radionuclide ventriculography and invasive cardiac monitoring, this study investigated the effects on LV performance in patients with stable chronic coronary artery disease of the emulsion preparation of propofol as a sole anesthetic agent and in combination with fentanyl.

Methods

Patients

After approval by our local ethics committee and after obtaining informed consent, 10 ASA III patients (51–75 years) undergoing major urologic surgery participated in this study. All patients had documented angina pectoris (NYHA II and III) secondary to coronary artery disease but none had a history of previous myocardial infarction, congestive heart failure, valvular heart disease, or hypertension. The diagnosis of coronary artery disease was established by the presence of typical angina pectoris brought on by effort and relieved by rest and nitroglycerin, and further documented by positive exercise tests. No patients were premedicated, but all received their usual medications (nifedipine and isosorbide) up to and including the morning of surgery to ensure a stable hemodynamic state before the procedure. The study was performed in the nuclear medicine laboratory just before surgery.

Invasive Monitoring

The following catheters were inserted percutaneously under local anesthesia: two 18-gauge catheters were placed into two forearm veins for administration of drugs and radionuclide red blood cells; a 7.5 French, thermodilution, Swan–Ganz catheter (93A-831-7.5Fr American Edwards Laboratories) was inserted into the pulmonary artery via an antecubital or internal jugular vein for measurement of RAP, PAP, PCWP, and thCO; a 20-gauge cannula was placed into the nondominant radial artery for monitoring arterial blood pressure and for blood sampling. Heart rate was measured from lead II of the ECG. Pressures and ECG were continuously displayed on a monitor and recorded on a polygraph (Siemens Sirecust 404-1). Thermodilution cardiac output was measured in triplicate within 1.5 minutes by the thermodilution technique after injection into the right atrium of 5 ml of 0°C 5% glucose solution (Siemens Sirecust 404-1). All thCO, RAP, PAP, and PCWP measurements were made at the end of expiration. Thermodilution cardiac output was indexed for body surface area as thCI. Systemic vascular resistance and SV were calculated using standard formulas (9) and indexed for body surface area, as SVRI and SI respectively. Systemic and mixed venous arterial blood samples were simultaneously withdrawn within 1 minute after CO measurements. Oxygen pressure, $\mathrm{Pco_2}$, pH, hemoglobin concentration, and hemoglobin saturation ($\mathrm{Sao_2}$ and $\mathrm{S\bar{v}_{O_2}}$) were measured with an ABL 300 Radiometer. Arterial oxygen content and $\mathrm{C\bar{v}_{O_2}}$, $\mathrm{a\text{-}\bar{v}_{O_2}}$, $\mathrm{\dot{V}o_2}$, and OER were calculated using standard formulas (9). Oxygen consumption was indexed for body surface area as $\mathrm{\dot{V}o_2I}$.

Isotopic Study

All patients were studied by radionuclide angiography using first-pass and ECG gated equilibrium blood-pool techniques with in vivo red blood cells labeled with ^{99m}Tc. The basic principle is that radioactivity recorded from the left ventricle in a left anterior oblique view is proportional to LV volumes after correction for absorption of radiation in the myocardium and the thoracic wall. The study was performed using a commercial scintillation camera equipped with an all-purpose, medium-resolution, medium-sensitivity collimator. The data were extracted from the modified left anterior oblique (40–45° from anterior, 10–15° caudal tilt) projection, and adjusted for maximal separation of the left ventricle from all other cardiac chambers and for optimal visualization of septum. A lyophilized solution containing 100 mg stannouspyrophosphate (TCK 7 CEA) was injected IV. Pretreatment with stannouspyrophosphate causes ^{99m}Tc to bind to the patient's red blood cells with 85–95% efficiency, thus retaining the tracer within the intravascular compartment. Thirty minutes later, an in vivo preparation containing 2 mCi of ^{99m}Tc pertechnetate (Technetium CEA Elumat 300) was counted 10 cm away from a gamma-camera.

A *first-pass study* was done after the IV injection of the above source, making possible the measurement of isCO using the Stewart Hamilton principle and the estimation of AF. Attenuation factor was assessed as the ratio Q/(C × MTT) where Q = injected counts/sec, C = integrated counts during the first transit, and MTT = mean transit time of the bolus through the left ventricle during the first transit.

A 20-mCi source was then injected and an *equilibrium study* was performed. Sixteen ECG-synchronized frames were acquired by a computer for processing: LV regions of interest were drawn on ED and ES images. Mean ED and ES counts, LVED and LVES areas, and EF were calculated for 1.5 minutes apiece. Halfway through data acquisition, a blood sample was withdrawn from a peripheral vein and counted. Exact numerical values in milliliters of EDV, ESV, SV, and deCO were then obtained by using a standard, radionuclide-based method formula: volume = (AF × N)/(t × X) where N = the intraventricular counting, t = the actual acquisition time, and X = the non-attenuated count rate of one volume unit of blood. Densitometric cardiac output and first-pass isCO were compared in each patient for validation of the method. The necessary time for each isotopic acquisition was fixed at 1.5 minutes, to be contemporaneous with the hemodynamic study to determine if there was a relation between isotopic densitometric and thermodilution SI.

The fact that the radioactive counts in a region are proportional to the amount of tracer allowed regional assessment of LV wall motion by *REF imaging,* which provides an objective, reproducible, and sensitive quantitative parameter for LV regional performance in patients with coronary artery disease (10). On a pixel (picture element)-by-pixel basis, dividing the stroke volume image (produced by subtracting the ES frame from the ED frame during a cardiac cycle) by the corresponding ED image produced an ejection fraction image, a map of regional ejection of the left ventricle. These functional images were displayed on a color scale where each color represented a 6% difference in REF and were broken down by the computer on a histogram into four classes: REF > 0.60, REF between 0.40 and 0.60, REF between 0.40 and 0 and REF < 0. Distribution in percent of these four classes of REF was then determined.

Protocol

Before the induction of anesthesia, a baseline set of hemodynamic and densitometric isotopic measurements (awake) was recorded. Anesthesia was then induced with propofol (2 mg/kg in 20 seconds), followed by an infusion of propofol (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Vecuronium (0.05 mg/kg) was administered and a manually controlled ventilation (FI_{O_2}, 1.0) was instituted to maintain FE_{CO_2} between 4% and 5% (47210 A Capnometer Hewlett-Packard). Six series of measurements, including hemodynamic and densitometric isotopic data, were then made between 1 and 2.5 (P1), 3 and 4.5 (P3), 6 and 7.5 (P6), 9 and 10.5 (P9), 12 and 13.5 (P12) and 15 and 16.5 minutes (P15). The last measurements (F) were made 5 minutes after the administration of fentanyl (5 μg/kg). Baseline arterial and mixed venous blood samples were obtained at baseline P3, P6, P15, and F for blood gas analysis. Arterial blood samples were obtained at each recorded points for measurement of propofol concentrations. Samples were placed into tubes that contained potassium oxalate and stored at 4°C before analysis. Whole blood propofol concentrations were measured after extraction into cyclohexane by a high-pressure liquid chromatographic method using fluorescence detection (11). The limit of sensitivity of the assay is approximately 2 ng/ml and the coefficient of variation over the concentration range measured is approximately 8%.

After the last of the data acquisitions described above, the trachea was intubated and the patient was moved into the operating room.

Statistical analysis

All data are given as mean ± SD. Analysis of variance and paired *t*-test with Bonferroni correction were used for statistical analysis. Correlations between specific variables were tested for significance with a linear regression method. $P < 0.05$ was considered significant.

Results

The more important results are summarized in Table 1. The administration of propofol followed by a maintenance infusion resulted in an average 15% decrease in MAP. This was associated with a decrease in CI without a decrease in SVRI. Despite the decrease in MAP, heart rate did not change. The decrease in CI was associated with decreases in EDV, in RAP, and in PCWP resulting in a decrease in preload. End systolic volume and EF did not change. Indexed oxygen consumption decreased 35%, accompanied with a decrease in $a\text{-}\bar{v}_{O_2}$ and OER. After the addition of fentanyl, MAP decreased significantly (35%) below the last propofol measurement (P15). The decrease in MAP was accompanied by decreases in CI and in SVRI. Fentanyl was associated with a significant decrease in heart rate (16%) resulting in a

Table 1. Hemodynamic Changes Associated with Propofol and Fentanyl Anesthesia

	Awake	P1	P3	P6	P9	P12	P15	P+F	ANOVA *P* value
Heart rate (beats/min)	71 ± 14	74 ± 8	73 ± 12	72 ± 13	72 ± 13	71 ± 12	68 ± 11	57 ± 8#	<0.05
MAP (mmHg)	100 ± 22	88 ± 22*	87 ± 22‡	85 ± 24‡	84 ± 23†	85 ± 25*	87 ± 22†	53 ± 9#	<0.001
MPAP (mmHg)	12 ± 2.8	9.2 ± 3‡	8.5 ± 2.8‡	8.5 ± 2.8‡	8.1 ± 2.9‡	8.3 ± 2.5‡	7.9 ± 2.5§	7.4 ± 2.8	<0.01
PCWP (mmHg)	6.1 ± 2	3 ± 2†	2.6 ± 2.2†	2.5 ± 2.7†	3 ± 2.7†	3.2 ± 2.9†	3.1 ± 3.1†	3.2 ± 2.8	<0.01
RAP (mmHg)	2.9 ± 1.3	0.6 ± 1§	0.7 ± 1§	0.6 ± 0.9§	0.8 ± 1.4‡	0.9 ± 1.3‡	0.8 ± 1.2‡	0.5 ± 0.7	<0.001
thCI ($1 \cdot min^{-1} \cdot m^{-2}$)	3.15 ± 0.68	2.64 ± 0.67*	2.42 ± 0.67‡	2.56 ± 0.8*	2.59 ± 0.73†	2.43 ± 0.73*	2.43 ± 0.88*	1.88 ± 0.55¶	<0.02
thSI ($ml \cdot beats^{-1} \cdot m^{-2}$)	45.6 ± 7.9	36.5 ± 8.2‡	33.8 ± 5.7‡	35.9 ± 7.2‡	36.3 ± 6.4‡	34.9 ± 7.7†	36 ± 9†	34.2 ± 7.6	<0.02
SVRI ($dynes \cdot sec \cdot cm^{-5} \cdot m^{-2}$)	2495 ± 432	2658 ± 780	2829 ± 749	2593 ± 689	2563 ± 610	2795 ± 880	2838 ± 860	2215 ± 491 ‖	<0.05
a-vo$_2$/mdl)	2.8 ± 0.97	—	1.92 ± 0.53†	1.98 ± 0.48*	—	—	2.06 ± 0.52†	3.21 ± 0.8#	<0.02
$\dot{V}o_2I$ ($mlO_2 \cdot min^{-1} \cdot m^{-2}$)	94 ± 32	—	47 ± 13‡	49 ± 9‡	—	—	49 ± 10	62 ± 24	<0.001
OER	0.17 ± 0.06	—	0.12 ± 0.04*	0.12 ± 0.03*	—	—	0.12 ± 0.03*	0.19 ± 0.04**	<0.001
EF (%)	55.4 ± 5.8	57.2 ± 6.2	56.9 ± 8.7	57.4 ± 8.7	58.2 ± 7.2	57 ± 7.7	57.6 ± 8.3	56.4 ± 5.1	NS
EDV (ml)	140 ± 22	130 ± 20†	129 ± 18†	131 ± 17*	131 ± 19*	129 ± 20†	130 ± 18*	127 ± 16	<0.001
ESV (ml)	61 ± 13	56 ± 14	56 ± 15	57 ± 17	56 ± 15	56 ± 16	56 ± 15	56 ± 11	NS
$PaCO_2$ (kPa)	4.74 ± 0.38	—	4.4 ± 0.49	4.64 ± 0.37	—	—	4.56 ± 0.28	4.44 ± 0.35	NS
Whole blood P (ng/ml)	0	6449 ± 2672	3118 ± 918	3200 ± 872	2791 ± 799	3111 ± 890	3165 ± 985	3028 ± 751	

All values are mean ± SD.

Abbreviations: P, propofol, 2 mg/kg IV, followed by propofol infusion, 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$; P + F, 5 minutes after fentanyl, 5 μg/kg IV, propofol infusion maintained; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; thCI, thermodilution cardiac index; thSI, thermodilution stroke index; SVRI, systemic vascular resistance index; a-$\dot{V}o_2$, arteriovenous difference in oxygen contents; $\dot{V}o_2I$, indexed oxygen consumption; OER, oxygen extraction ratio; EF, global ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; $Paco_2$, arterial carbon dioxide pressure; NS, not significant.

*$P < 0.05$, compared to awake value; †$P < 0.02$, compared to awake value; ‡$P < 0.01$, compared to awake value; §$P < 0.001$, compared to awake value; ‖ $P < 0.05$, compared to P15 value; ¶$P < 0.02$, compared to P15 value; #$P < 0.01$, compared to P15 value; **$P < 0.001$, compared to P15 value.

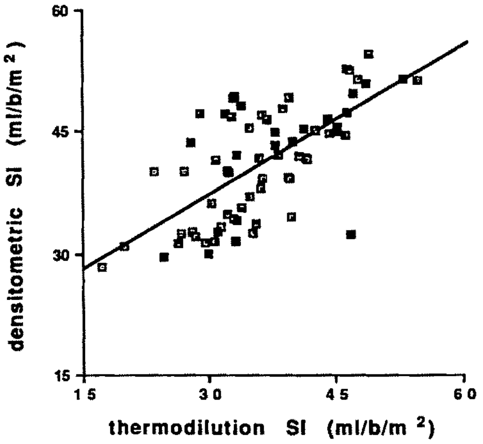

Figure 1. Linear relationship between stroke index values measured by thermodilution technique and isotopic densitometric method. $n = 70$; $y = 0.61x + 19.068$; $r = 0.68$; $P < 0.001$.

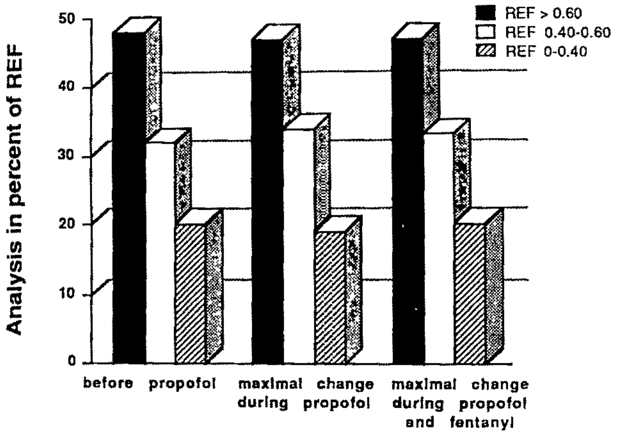

Figure 2. Analysis in percent of regional ejection fraction (REF). On a pixel-by-pixel basis, regional ejection fraction images are broken down into three classes: REF > 0.60, REF between 0.60 and 0.40, REF between 0.40 and 0. Each class is expressed in percentage of total number of pixels in the left ventricular area before and after propofol and fentanyl administration.

decrease in CI but without changes in SI and preload. Indexed oxygen consumption remained unchanged but a-$\bar{v}_{O_2}$ and OER increased 60%. Body temperature remained unchanged throughout the procedure (range 36.3– 37.2°C). There was a significant linear relationship between SI measured by the thermodilution technique and isotopic densitometric SI ($y = 0.61x + 19.068$; $n = 70$; $r = 0.68$; $P < 0.001$) (Fig. 1). No ECG changes occurred during the procedure in any patient. Finally, neither EF nor REF changed significantly (Fig. 2).

Discussion

Comparison of our findings with those of other investigators is difficult because of variations in anesthetic technique, condition of the patients, preoperative drug therapy, and premedication. Several aspects of the methods we used require comment. The ED_{50} infusion rate (the dose required to prevent movement during surgical incision in 50% of patients) for an intravenous anesthetic provides a logical and useful starting point for the investigation and comparison of hemodynamic effects of intravenous anesthetics (12). To allow identification of features of the hemodynamic responses to intravenous infusion of propofol we used an infusion rate of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which is double the ED_{50} of propofol (13). In our study, plasma concentrations of propofol were similar to those found by Coates et al. (14) and Monk et al. (15) at similar infusion rates. An important premise in these studies, as well as in ours, is that a clinically stable depth of anesthesia and a near pharmacologic steady state had been achieved, although, according to the pharmacokinetic data published by Cockshott (16), even after a 4-hour infusion, blood levels of propofol would remain below steady state values. To distinguish the hemodynamic effects of both drugs used in our subjects from the effects of painful stimuli, our study was conducted before surgery and without tracheal intubation, FE_{CO_2} and $Paco_2$ remaining constant with manual ventilation and a face mask. Our patients were not premedicated; consequently, the existence of basal rest conditions at the baseline point may be disputed, although invasive monitoring catheters were placed at least one hour before the procedure and patients rested for at least 30 minutes during pretreatment with stannouspyrophosphate.

The effect of propofol on heart rate is still controversial. In our study and those of Prys-Roberts et al. (5) and Cummings et al. (13), heart rate remained unchanged. Aun and Major (17), in patients with valvular heart disease, and Patrick et al. (6), in patients with ischemic heart disease, both observed a decrease in heart rate. Stephan et al. (2) and Al-Khudairi et al. (18), in patients with coronary artery disease, reported, on the other hand, a significant increase in heart rate. Reasons for these differences are not clear. Heart rate may increase during propofol administration if there is an increase in sympathetic nervous system activity associated with nitrous oxide anesthesia (19). The fact that heart rate did not increase despite a decrease in MAP has been explained by Samain et al. (20) and by Cullen et al. (21) as being due to the fact that propofol does not impair the baroreflex sensitivity but instead resets baroreflex control of heart rate, which results in a lower level of arterial pressure for a given heart rate. In our study, the addition of fentanyl to propofol infusion led to a further decrease in heart rate: the negative chronotropic effect of fentanyl is enhanced by the effect of propofol on baroreflex function. In our experience atropine was usually effective in treating propofol–fentanyl induced bradycardia.

Our results demonstrate that propofol used alone significantly decreases MAP, CI and preload without changing heart rate or SVRI. The combination of propofol with fentanyl resulted in further decreases in CI and MAP secondary to decreases in heart rate and SVRI. It is important to note that propofol anesthesia resulted in a 50% decrease in $\dot{V}o_2I$ as well as decreases in CI and a-$\bar{v}_{O_2}$. The fact that a-$\bar{v}_{O_2}$ decreased simultaneously with a decrease in OER, an index of the efficacy of the circulation, suggests that the decrease in $\dot{V}o_2I$ was due mainly to a decrease in oxygen demand, the latter contributing to the decrease in CI. Cardiac output is adjusted to a lower metabolic rate. After the injection of fentanyl, $\dot{V}o_2I$ remained below awake levels, while CI continued to decrease and a-$\bar{v}_{O_2}$ and OER increased. Whether an inadequate oxygen delivery, i.e., demand out of proportion to supply, was involved, resulting in a deleterious effect on cellular metabolism, cannot be determined because lactate levels were not measured.

When propofol in the emulsion formulation was used alone in the present study, the reduction in MAP observed on induction and during the maintenance infusion was comparable to previous data (2,5,6,14,15,18). The simultaneous decreases in SI and in ventricular filling volumes and pressures strongly suggest a decrease in venous return due to an increase in venous capacitance. In our study the decrease in MAP was exclusively due to a decrease in CI without change in SVRI, results similar to those reported by Stephan et al. (2). Because SVRI remained unchanged despite the decrease in CI, it can be assumed that propofol produces arteriolar vasodilation. The differences in published data on the effects of propofol on SVR are probably related for the most part to conditions of vascular tone before injection of propofol. Our patients took their cardiac medications until the morning of the study, and this may have influenced hemodynamic responses. Whether propofol decreases predominantly the arterial or the venous tone is unknown: the initial decrease in SI observed in our patients may reflect a predominant vascular effect on the venous side, because the expected increase in CI after arteriolar dilation did not occur.

The addition of fentanyl to propofol infusion led to a further significant decrease in MAP associated with a decrease in CI (but not in SI and preload) and a reduction in SVRI. Similar findings were reported by Vermeyen et al. (1), but in the Stephan et al. series (2), preload decreased while afterload was unaffected.

Despite the relatively large decreases in MAP and in CI seen in our patients with coronary artery disease, there was no evidence of LV depression or development of myocardial ischemia with either propofol alone or with the propofol–fentanyl combination.

Global ejection fraction, considered to be a good index of heart pump function, remained stable in our study. However, myocardial contractility, as well as both preload and afterload, affect EF, decreases in afterload modifying pump function by enhancing ejection. Ventricular ES volume varies inversely and ES pressure varies directly with contractility. The fact that CI and SI did not increase and ESV did not decrease when MAP decreased may support the conclusion that propofol–fentanyl anesthesia has potent depressive properties on LV function. Nevertheless, 1) SVR is not a reliable index of LV afterload (22), reflecting only the nonpulsatile component of peripheral arteriolar tone, rather than the LV systolic wall force; 2) MAP in the radial artery does not represent LVES pressure; 3) the decrease in preload observed during propofol anesthesia should create a change in the same direction of CO, provided myocardial performance and ventricular afterload remain the same; and, 4) heart rate, which decreased during propofol–fentanyl combination, is a major component of contractility. The present data thus do not necessarily reflect depression of cardiovascular function.

In addition, there was no evidence of impairment of either coronary perfusion or myocardial oxygenation. Electrocardiograms remained unchanged, though it must be understood that, even in the absence of ST depression, the heart can become ischemic and produce lactate, as occurred in one patient in the study of Stephan et al. (2). Finally the absence of variation in the distribution of REF, an indirect index of ischemic depression of myocardial contraction, was in favor of the maintenance of myocardial oxygenation in our patients.

We conclude that propofol alone and in combination with fentanyl in 10 patients with coronary artery disease and good LV function, maintained preoperatively with nitrates and calcium-channel blocking drugs, did not alter LV performance and that the myocardial oxygen supply/need relationship was maintained. However, in patients with coronary artery disease, the magnitude of the arterial pressure reduction, particularly after fentanyl injection, is cause for concern. Coronary perfusion might be jeopardized in patients with severe ischemic heart disease leading to myocardial ischemia or infarction.

We are indebted to JL Harmey, MD and to ICI Pharma, Cergy, France, for supplies of propofol.

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ANESTH ANALG
1988;67:956–60

Age Has No Effect on the Pharmacodynamics of Alfentanil

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LEMMENS HJM, BOVILL JG, HENNIS PJ, BURM AGL. Age has no effect on the pharmacodynamics of alfentanil. Anesth Analg 1988; 67:956–60.

Effects of age on the pharmacodynamics of alfentanil, as a supplement to nitrous oxide anesthesia, were studied in younger (31–52 years; n = 14) and older (56–86 years; n = 14) women undergoing curative surgery for primary breast cancer. Plasma alfentanil concentration–effect curves for perioperative stimuli and for the probability of needing naloxone at the end of the operation were fitted by logistic regression. Effects of age on the plasma concentration–effect relation of alfentanil could not be demonstrated. However, the dose requirement in the older patient group was significantly lower than in the younger patient group.

Key Words: ANALGESICS—alfentanil. ANESTHETICS—intravenous, alfentanil. PHARMACODYNAMICS—age, alfentanil. AGE FACTORS—alfentanil pharmacokinetics.

The dose requirements for opioids are lower in the elderly than in younger patients (1). This can be due either to age-related changes in the pharmacokinetic or to the pharmacodynamic properties of these drugs.

Helmers et al. (2) demonstrated that the plasma clearance of alfentanil is less rapid and the elimination half-life is longer in elderly patients than in young patients. Scott and Stanski (3) also found that the elimination half-life of alfentanil increased with increasing age, but did not find any change in the clearance of alfentanil. The same authors investigated the effects of age on the pharmacodynamics of alfentanil, using the EEG as a measure of effect. They demonstrated that the alfentanil plasma concentration producing 50% of the maximal shift in the spectral edge of the EEG (IC50) decreases with increasing age. This suggests that elderly patients are more sensitive to the central nervous effect of alfentanil. The clinical implications of these findings are not clear. No data are available on the effects of age on the relationship between plasma concentration of alfentanil and response to stimuli during anesthesia and surgery.

We studied the effects of age on the plasma concentration–effect relation of alfentanil, in a clinical situation, using clinical criteria (probability of suppressing responses to perioperative stimuli) as a measure of effect.

Patients and Methods

After approval by the local Committee on Medical Ethics and obtaining informed consent, two groups of patients (ASA status 1 or 2) were studied. Patients in group I ($n = 14$) were 31–52 years old and patients in group II ($n = 14$) were 56–86 years old (Table 1). All patients were women undergoing curative surgery for primary breast cancer. All had normal hepatic and renal function, and none had a history of cardiac, pulmonary, or neurological disease. None of the patients was receiving medication or had a history of alcohol or other drug abuse.

Alfentanil was administered by a computer-controlled infusion pump (TIAC: Titration of Intravenous Agents by Computer; Janssen Scientific Instruments, Janssen Pharmaceutica, Belgium). This system, which was supplied with age-adjusted pharmacokinetic data (2,4), allows a target plasma concentration of alfentanil to be rapidly attained, maintained, or altered. If the target plasma concentration is increased, the new set point is theoretically achieved within 6 sec.

Premedication was with oral temazepam, 10–20 mg, 1 hour and intramuscular atropine, 0.25–0.5 mg,

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Supported by Janssen Pharmaceutica, Beerse, Belgium.

Received from the Department of Anesthesiology, University Hospital, Leiden, The Netherlands. Accepted for publication May 10, 1988.

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Table 1. Patient Characteristics*

	Group I (<55 years)	Group II (>55 years)
Number of patients	14	14
Age (years)	44 ± 7	70 ± 10
Weight (kg)	64 ± 7	68 ± 10
Duration of anesthesia (minutes)	154 ± 29	154 ± 25
Percent of anesthesia time with response to fourth stimulus of train of four	91 ± 7	93 ± 6
Total alfentanil dose ($\mu g \cdot Kg^{-1} \cdot min^{-1}$)	2.21 ± 0.68	1.68 ± 0.52†

*Data are mean ± SD.
†Difference between group I and group II: $P < 0.05$.

0.5 hour before surgery. Upon arrival in the operating room ECG electrodes were placed. A 20-gauge cannula was inserted in a radial artery for continuous measurement of blood pressure and collection of blood samples. Before induction of anesthesia, 300–500 ml of 0.9% sodium chloride solution was infused. Pancuronium, 0.02 mg/kg, was given to prevent muscle rigidity and the patients were preoxygenated. After 3 minutes, the fresh gas flow was changed from 100% oxygen to 66% nitrous oxide in oxygen. Simultaneously, an infusion of alfentanil was started. The target alfentanil plasma concentration for induction of anesthesia was 350 ng/ml, to be achieved in 2 minutes. When the patient lost consciousness, succinylcholine, 1 mg/kg, was given, and the patient was ventilated by mask with 66% nitrous oxide in oxygen. The trachea was intubated 6 minutes after starting the alfentanil infusion. After intubation, the target alfentanil plasma concentration was lowered to 200 ng/ml. Ventilation was adjusted to maintain end-tidal carbon dioxide concentration between 4 and 5 vol%.

If the patient showed signs of inadequate anesthesia, the target alfentanil plasma concentration was increased by 50–100 ng/ml. If necessary, this was repeated every 5 minutes. Inadequate anesthesia was defined by the following criteria:

1. Increase in systolic blood pressure by more than 15 mm Hg above normal for that patient. Normal was defined as the lowest pressure measured in the time from admission to the hospital until just before premedication.
2. A heart rate greater than 90 beats/min in the absence of hypovolemia.
3. Other autonomic signs such as sweating, flushing or epiphora.
4. Somatic responses such as movements, swallowing, coughing, grimacing or eye movement.

If a patient did not respond during a 15-minute period the target plasma concentration was lowered by 50 or 100 ng/ml.

To facilitate identification of a somatic response, pancuronium was given at a minimal dose. Neuromuscular blockade was monitored using the train of four method by percutaneous stimulation of the facial nerve (Myotest: Odense, Denmark). Each patient received a maintenance infusion of 300–500 ml/hr 0.9% sodium chloride solution, supplemented by a volume equal to the blood loss. Blood loss was measured at least every 15 minutes during surgery. It did not exceed 450 ml for the total surgical procedure in any patient.

At the end of surgery nitrous oxide was discontinued and residual neuromuscular blockade reversed (if indicated) with atropine (0.5 mg) and neostigmine (1 mg). Patients were extubated after recovering consciousness and when adequate ventilation was established (frequency > 10 breaths/min, end-tidal $CO_2 < 6.5$ vol%, tidal volume > 7 ml/kg). If, 10 minutes after discontinuation of nitrous oxide, ventilation was not adequate, naloxone 0.04 mg, IV, was given every 3 minutes until ventilation became adequate without verbal encouragement.

Arterial blood samples for the measurement of alfentanil plasma concentrations were collected before induction of anesthesia, before intubation, and before skin incision. Additional samples were taken before any change in the target alfentanil plasma concentration and 4 and 15 minutes after a target plasma concentration was achieved. In patients in whom ventilation recovered spontaneously, a blood sample was taken immediately before extubation. In the remaining patients a sample was taken 10 minutes after discontinuation of nitrous oxide, before administration of naloxone.

Plasma concentrations of alfentanil were measured by capillary gas chromatography. The coefficient of variation did not exceed 5% in the concentration range concerned.

Data Analysis

The presence or absence of a response (or the need for naloxone), and the corresponding measured plasma concentration were entered in a logistic regression computer program, ELSFIT (5), which fitted the data to the following equation:

$$\text{Probability of no response} = \frac{Cp^{\gamma}}{Cp50^{\gamma} + Cp^{\gamma}}$$

Cp is the measured plasma alfentanil concentration, where Cp50 is the concentration at which probability of no response is 0.5, γ is a dimensionless parameter reflecting the slope of the response curve.

The Cp50 values for intubation, skin incision, and the probability of needing naloxone at the end of the operation, were calculated for both groups. Individual Cp50 values for surgical stimulation during the procedure were determined for each patient.

Data are reported as mean ± SD and as the incidence of observations, unless specified otherwise. A two sample *t*-test or Fisher's exact test were used for intergroup comparisons. Linear regression analysis was used to examine the correlation between age and Cp50 for the surgical operation. $P < 0.05$ was regarded as statistically significant.

Results

The groups were comparable with respect to weight, duration of anesthesia, and the percentage of anesthesia time during which a response to the fourth stimulus of the train of four was present (Table 1).

All patients lost consciousness within 2 minutes after starting the alfentanil infusion. However, induction of anesthesia was associated with several side effects. Hypotension, defined as a decrease in systolic blood pressure more than 15 mm Hg below normal, occurred in three patients in group II. The lowest systolic blood pressures for each were 80, 80, and 90 mm Hg. Decreases in blood pressure were restored to normal before intubation by administration of IV ephedrine, 7.5 mg, and rapid infusion of 200–300 ml saline. In one patient, in whom hypotension was associated with a bradycardia of 42 beats/min, heart rate and blood pressure were rapidly restored to preinduction values after IV administration of atropine, 0.25 mg. Hypotension did not occur in group I. Heart rates lower than 45 beats/min without hypotension occurred in one patient in group I (44) and in three patients in group II (31, 42, and 38 beats/min). These were successfully treated with IV atropine, 0.25 mg. One patient in group I and six patients in group II developed muscle rigidity. In one patient in group II ventilation was not possible until succinylcholine had been given. The difference in the occurrence of muscle rigidity between groups was statistically significant (Fisher's exact test, $P < 0.05$). None of these side effects recurred during anesthesia.

The calculated Cp50 values for intubation, skin incision and the probability of needing naloxone at the end of operation in groups I and II are shown in Table 2. The corresponding plasma concentration versus probability curves are shown in Figures 1 and 2. The Cp50 values for the surgical operation for each patient are shown in Table 3. The average Cp50 in group I (256 ± 90 ng/ml) was not statistically different from the average Cp50 in group II (280 ± 133 ng/ml). There was no correlation between Cp50 and age (Fig. 3). The plasma concentration vs probability of no response curves for the surgical operation of each patient in both groups are shown in Figure 4.

Table 2. Cp50 and γ for Intubation, Skin Incision and Probability of Needing Naloxone

	Group I		Group II	
	Cp50 (ng/ml)	γ	Cp50 (ng/ml)	γ
Intubation	440	9.2	441	5.0
Skin incision	226	3.3	196	2.8
Probability of needing naloxone	272	3.8	226	3.0

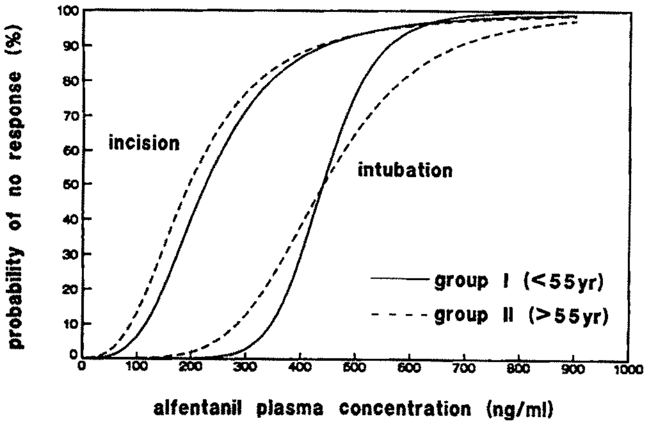

Figure 1. Relationship between measured alfentanil plasma concentration and probability of no response to intubation and skin incision.

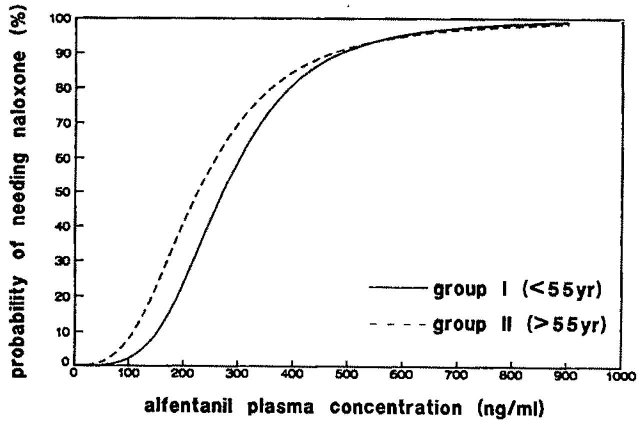

Figure 2. Relationship between measured alfentanil plasma concentration and probability of needing naloxone to restore spontaneous ventilation.

Table 3. Cp50 and γ for the Surgical Operation in Individual Patients

	Group I		Group II	
	Cp50 (ng/ml)	γ	Cp50 (ng/ml)	γ
	235	4.1	335	16.0
	199	99.9	180	2.2
	212	8.0	161	30.7
	247	3.1	474	6.6
	178	99.0	232	6.4
	384	3.2	352	6.0
	312	7.0	635	10.6
	171	7.8	257	4.9
	193	3.5	218	3.2
	223	9.9	151	99.9
	203	16.2	215	3.5
	425	12.2	263	6.2
	414	2.9	236	99.9
	182	99.9	214	93.4
mean ± SD	256 ± 90		280 ± 133	

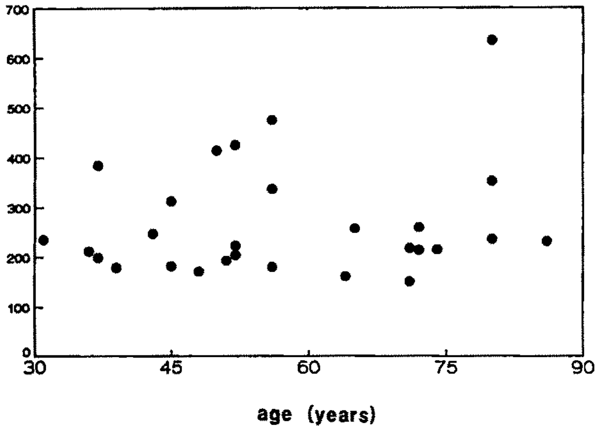

Figure 3. Individual Cp50 values for the surgical operation of each patient versus age ($r = 0.15$; $n = 28$).

The type and number of responses observed during the study are given in Table 4. All responses were rapidly controlled by increasing the target alfentanil plasma concentration. Systolic blood pressure returned to normal within 1–8 minutes (median 2 minutes) in group I and within 1–7 minutes (median 2 minutes) in group II. Heart rate returned to normal within 1–2 minutes (median 1 minute) in both groups.

Naloxone was needed to restore adequate spontaneous ventilation in four patients in group I (average dose, 0.05 ± 0.02 mg), and in five patients in group II (average dose, 0.07 ± 0.03 mg).

The alfentanil dose requirement was significantly lower in group II (Table 1).

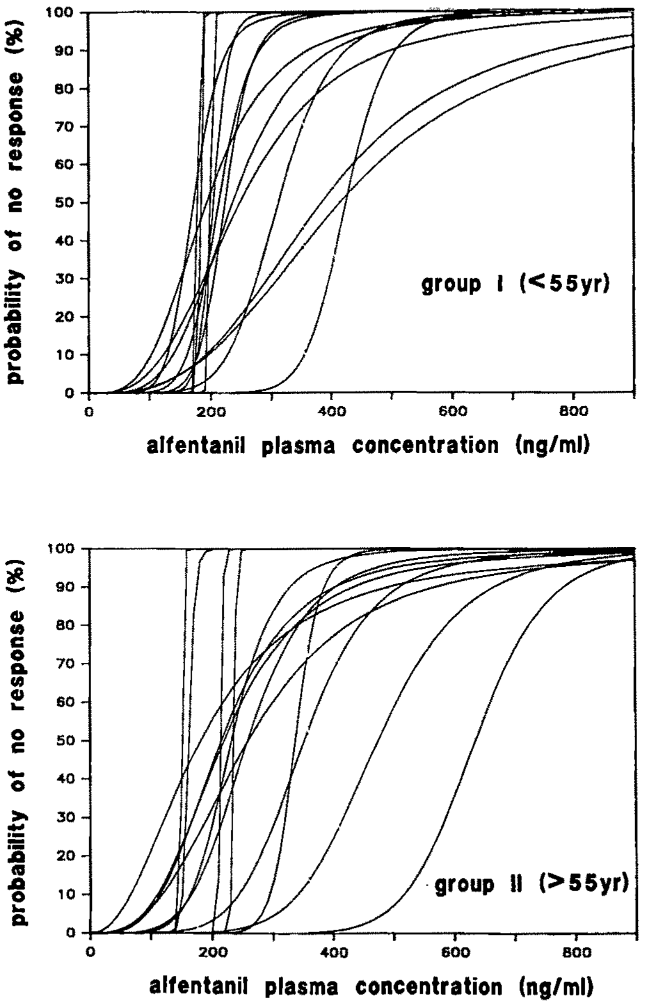

Figure 4. Curves of measured alfentanil plasma concentration versus probability of no response for each patient during surgery.

Table 4. Type and Number of Responses to Perioperative Stimuli

Response	Group I	Group II
Systolic blood pressure above normal + 15 mm Hg	36	47
Heart rate above 90 beats/min	10	2
Somatic responses	28	17
Other responses	1	0

Discussion

Pharmacodynamic studies in which plasma concentrations are not maintained at a steady state are complicated by hysteresis, i.e., a time lag between plasma concentration and effect. In this study plasma concentration–response relationships were determined as far as was possible after allowing time for equilibration between plasma and brain concentration. The hysteresis effect with alfentanil ($t_{½}K_{eo} = 0.9 \pm 0.3$ minutes) is significantly less than with fentanyl ($t_{½}K_{eo} = 4.7 \pm 1.5$ minutes), without age dependent changes (3). Scott and Stanski (3) evaluated the rate of blood-brain equilibration using the EEG as a parameter of effect. Their data are probably also valid for other effect parameters, such as signs of light anesthesia. Brain concentrations are expected to reach equilibrium within approximately 3–4 K_{eo} half-lives after a stable plasma concentration has been attained, i.e., within approximately 4 minutes in the case of alfentanil. Thereafter, a stable plasma concentration can be expected to reflect the concentration of alfentanil at the receptor-site. The TIAC device, used in our study, has been shown to maintain relatively stable plasma concentrations (6,7). However, some responses occurred during changing plasma concentrations, i.e., after decreasing the target alfentanil plasma concentration, and at the end of surgery when plasma concentrations were declining.

In contrast to the findings of Scott and Stanski (3) we could not demonstrate any effect of age on the plasma concentration–effect relation of alfentanil. The average Cp50 for the surgical procedures did not differ between the younger and older patient groups. There was also no correlation between the Cp50 for the surgical procedure in individual patients and their ages. The Cp50 values for intubation, skin incision, and the probability of needing naloxone were similar in both groups. These values, however, were derived from the combined data of all patients in each group, because only one data point was available for each patient. Although the computer program provided some indication of the accuracy (standard error) of the Cp50 values, this figure usually underestimates the true standard error and should not be used for statistical purposes. The Cp50 values reported in our study are similar to those reported by Ausems et al. in young adult patients (8).

We observed significantly more muscle rigidity during induction of anesthesia in the older patient group. We can only speculate as to whether this was due to alterations in the pharmacokinetics or in the pharmacodynamics of alfentanil. We did not measure the alfentanil plasma concentration at the time of the occurrence of muscle rigidity, which was 1–2 minutes after starting the alfentanil infusion. Plasma concentrations were measured just before intubation of the trachea, approximately 4–5 minutes after muscle rigidity occurred. It is therefore impossible to decide whether the higher incidence of muscle rigidity was due to alterations in the pharmacokinetics or in the pharmacodynamics of alfentanil.

It is generally assumed that drugs should be given in reduced doses in elderly patients. In this study the dose requirement for alfentanil in the younger patients was significantly higher than in the older patients. The pharmacodynamics of alfentanil were similar in both patient groups. This suggests that pharmacokinetic differences may be responsible for the decreased dose requirement in elderly patients.

The authors thank Mrs M. P. R. R. Gladines, Mrs A. E. Muller-de Ruiter and Mr A. A. Vletter for their assistance with the laboratory investigations and Miss W. C. E. van Leeuwen and Miss M. P. M. Toelen for typing the manuscript.

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ANESTH ANALG 961
1988;67:961–6

Pharmacokinetics of Bupivacaine after Short and Prolonged Infusions in Conscious Dogs

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MAZOIT JX, LAMBERT C, BERDEAUX A, GERARD J-L, FROIDEVEAUX R. Pharmacokinetics of bupivacaine after short and prolonged infusions in conscious dogs. Anesth Analg 1988;67:961–6.

A conscious dog model was used to study pharmacokinetics of bupivacaine after a short infusion (SI) (15 min) and a prolonged infusion (PI) (24 hours). Bupivacaine was infused in six mongrel dogs at least 10 days after implantation of femoral arterial and venous catheters. Each dog received both the SI and the PI in a random crossover design at a one week interval. Bupivacaine concentration was measured in serum sampled during the SI, during the last hour of the PI, and at frequent intervals during eight hours after cessation of infusion. Indocyanine green (ICG) clearance also was measured during the last hour of the PI and 90 min after cessation of both the SI and the PI. The terminal half-life ($T_{1/2_Z}$) *of bupivacaine increased after the PI compared with the SI, 167 ± 86 vs 53 ± 13 min, respectively (mean ± SD;* $P < 0.05$*), and total body clearance (Cl) decreased, 3.4 ± 1.2 vs 9.5 ± 4.5* $ml \cdot min^{-1} \cdot kg^{-1}$*,* ($P < 0.05$)*, although the volumes of distribution* (V_Z *and* V_{SS}) *did not change. A decrease in hepatic blood flow did not cause the decrease in Cl because ICG clearance did not change during the three sets of measurements. Thus, the observed increase in* $T_{1/2_Z}$ *and decrease in Cl after the PI as compared with the SI are due to a decrease in hepatic intrinsic clearance of bupivacaine. Differences in the kinetic profile of the two enantiomers of bupivacaine cannot be excluded as a cause. We conclude that the extrapolation of kinetic data of bupivacaine obtained after a short infusion (or a bolus injection) to prolonged dosage must be done with care.*

Key Words: PHARMACOKINETICS—local anesthetics, bupivacaine. ANESTHETICS, LOCAL—bupivacaine.

Regional blocks using bupivacaine are commonly used for intraoperative anesthesia as well as for postoperative and chronic pain relief (1). However, information regarding the pharmacokinetics of bupivacaine during prolonged administration is limited and contradictory. Denson et al. (2) suggested that bupivacaine clearance did not change significantly between 3–5 hours after the start of an infusion and its termination several days later. On the other hand, Raj et al. (3) observed an increase in bupivacaine plasma concentrations during the first 3 days of bupivacaine infusion, despite a decrease in dosage, in non-steady-state patients treated for postoperative pain relief. Furthermore, lidocaine has been shown to have time-dependent kinetics both in dogs and in humans (4,5). Thus, the question of time-dependent kinetics of bupivacaine presently remains unanswered. Because it is not possible to perform IV administration of bupivacaine in humans for ethical reasons, and to avoid the problems associated with pharmacokinetic studies performed under general anesthesia, we studied the pharmacokinetics of bupivacaine in conscious dogs. Using each animal as its own control, short (15-

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Supported in part by a grant from Roger Bellon Laboratories.

Received from the Departments of Anesthesiology and Pharmacology, Université Paris-Sud, Hôpital Bicêtre, France. Accepted for publication May 9, 1988.

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Abbreviations: SI, Short infusion (15 minutes); PI, Prolonged infusion (24 hours); k_1, Rate of infusion for the SI, rate of first infusion for the PI; k_2, Rate of second infusion of the PI; T_i, Duration of infusion for the SI (15 min); T_i1, Duration of first infusion for the PI (15 min); T_i2, Duration of second infusion for the PI (24 h); k_{12}, Rate constant from central to peripheral compartment; k_{21}, Rate constant from peripheral to central compartment; λ_1, Hybrid rate constant (initial phase); λ_z, Hybrid rate constant (terminal phase); C_{max}, Observed maximum concentration; C_{ss}, Steady-state concentration; V_c, Volume of the central compartment; V_{ss}, Steady-state volume of distribution; V_z, Apparent volume of distribution; Cl, Total body clearance; Cl_I, Intrinsic hepatic clearance; Cl_I', Intrinsic hepatic clearance of free drug; $T_{1/2_z}$, Terminal half-life; ICG, Indocyanine green.

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minute) and prolonged (24-hour) infusions of bupivacaine with simultaneous measurement of indocyanine green clearance were performed in a random crossover design.

Materials and Methods

In six mongrel dogs weighing 21 ± 5 kg (mean ± SD) femoral arterial and venous catheters were implanted using ketamine anesthesia. Patency of the catheters was maintained with heparin injections, 100–200 IU, once daily. The femoral arterial catheter was used for obtaining blood samples and the femoral venous catheter for infusions. After at least 10 days' recovery, each dog received, in a random crossover manner, a short and a prolonged infusion of bupivacaine separated by a one week interval. Randomization was done to obtain a block design, three dogs received the short infusion (SI) first and the other three received the prolonged infusion (PI) first. The SI consisted of infusion of bupivacaine, 1.5 mg/kg, in 15 minutes. The PI consisted of two successive infusions of bupivacaine: 0.5 mg/kg in 15 minutes followed by 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ for 23 hours 45 minutes. The PI was performed with a portable pump (Grasby Medical) attached to each dog's back; the dogs were allowed to move, drink and eat as usual. The time of cessation of infusion was the same (10 AM) in all experiments, because diurnal changes in bupivacaine kinetics have been demonstrated in rats (6).

Sampling and Analysis

Arterial blood samples (1 ml) were drawn 0, 3, 5, 10 and 13 minutes after the beginning of the SI and 0, 3, 5, 10, 15, 20, 30, 40, 60, and 90 minutes and 2, 3, 4, 5, 6, 7, and 8 hours after cessation of the SI. Arterial blood (1 ml) was sampled at 0, 15, 30 and 45 minutes during the last hour of the PI and 0, 3, 5, 10, 15, 20, 30, 40, 60 and 90 minutes and 2, 3, 4, 5, 6, 7 and 8 hours after cessation of the PI. Indocyanine green (ICG), 0.75 mg/kg, was injected as a bolus during the last hour of the PI and 90 minutes after cessation of both the SI and the PI. Arterial blood was sampled before (10 ml) and 2, 5, 8, 11 and 15 minutes (2 ml) after ICG bolus injection.

Bupivacaine concentration was measured in aliquots of 200 μl of serum using a Varian 3400 gas chromatograph equipped with a nitrogen-specific detector and a 3m × 2 mm ID glass column, fitted with 3% OV 11 on 100/120 mesh chromosorb W, AW, DMCS. Etidocaine was used as the internal standard and a single extraction in toluene was performed (7). ICG concentration was measured by spectrophotometry at 805 nm (8).

Pharmacokinetic Analysis and Statistics

Concentration-time data for bupivacaine were fitted to a two-compartment open model using nonlinear regression analysis (PCNONLIN) (9) as follows (10):

$$C = (k_1/V_c)\left\{\frac{(k_{21}-\lambda_1)}{\lambda_1(\lambda_1-\lambda_z)}(1-e^{\lambda_1 T})\,e^{-\lambda_1 t} - \frac{(k_{21}-\lambda_z)}{\lambda_z(\lambda_1-\lambda_z)}(1-e^{\lambda_z T})\,e^{-\lambda_z t}\right\}$$

after the SI and,

$$C = (1/V_C)\left\{\frac{(k_{21}-\lambda_1)}{\lambda_1(\lambda_1-\lambda_z)}(k_1(1-e^{\lambda_1 T_1}) + k_2(e^{\lambda_1 T_1} - e^{\lambda_1 T_2}))\,e^{-\lambda_1 t} - \frac{(k_{21}-\lambda_z)}{\lambda_z(\lambda_1-\lambda_z)}(k_1(1-e^{\lambda_z T_1}) + k_2(e^{\lambda_z T_1} - e^{\lambda_z T_2})\,e^{-\lambda_z t}\right\}$$

after the PI. With T = t during the SI and T_i after cessation of the SI.

T1 = t during the first infusion of the PI and T_i1 after cessation of the first infusion.
T2 = t during the first and the second infusions of the PI and T_i2 after cessation of infusion.

The following parameters were calculated as:

$$T_{1/2_Z} = 0.693/\lambda_Z$$

$$V_{SS} = V_c(k_{12} + k_{21})/k_{21}$$

$$V_Z = Cl/\lambda_Z$$

$$Cl = V_c(\lambda_1 \cdot \lambda_Z)/k_{21}$$

$$\text{or } Cl = k_2/C_{SS}$$

λ_Z was also calculated using log-linear regression of the observed terminal phase. Data are expressed as the mean ± SD. A Wilcoxon test for paired data was used to compare the kinetic parameters after the SI and the PI. The three sets of ICG clearance were compared using two-way analysis of variance.

Results

Parameters calculated from the concentration-time data are presented in Tables 1 and 2. Differences in the

Table 1. Parameters Estimates Obtained in the Six Dogs after SI and PI*

Dog	Weight (kg)		r	V_c (L)	k_{21} (min^{-1})	λ_1 (min^{-1})	λ_z (min^{-1})
1	25	SI	0.990	2.85 (0.8)	0.0357 (25)	0.1034 (14)	0.0133 (14)
		PI	0.979	2.50 (17)	0.0099 (28)	0.0514 (3)	0.0047 (11)
2	16	SI	0.989	3.68 (7)	0.0713 (24)	0.2361 (17)	0.0176 (17)
		PI	0.988	0.53 (23)	0.0758 (30)	0.2290 (35)	0.0086 (14)
3	16	SI	0.991	4.45 (4)	0.0195 (34)	0.0774 (10)	0.0097 (22)
		PI	0.988	0.99 (9)	0.0036 (68)	0.0783 (13)	0.0026 (5)
4	23	SI	0.989	2.28 (10)	0.0977 (12)	0.3977 (17)	0.0149 (6)
		PI	0.973	1.15 (11)	0.0060 (26)	0.1617 (28)	0.0024 (13)
5	19	SI	0.985	3.33 (2)	0.0553 (23)	0.1823 (16)	0.0163 (13)
		PI	0.971	3.32 (29)	0.0147 (123)	0.0812 (19)	0.0056 (18)
6	27	SI	0.988	10.45 (10)	0.0537 (44)	0.0870 (41)	0.0103 (14)
		PI	0.983	2.46 (28)	0.0404 (21)	0.1532 (40)	0.0066 (20)
Mean	21	SI		4.51	0.0555	0.1806	0.0137
		PI		1.82	0.0251	0.1258	0.0067
SD	5	SI		3.00	0.0273	0.1230	0.0032
		PI		1.09	0.0282	0.0670	0.0024
				$P < 0.05$	NS†	NS†	$P < 0.05$

*r is the correlation between observed and calculated values. The values in brackets are the coefficient of variation of each parameter (% CV), where CV was calculated as the ratio of the asymptotic standard deviation to the estimate of parameter. Other parameter abbreviations in text.

†NS, not significant.

values of λ_Z calculated by the two methods were always less than 7%; the values used for the calculations and reported in Table 1 are from nonlinear fitting. After the SI, the decline in serum concentration was rapid (Fig. 1). After the PI, the concentration at steady-state (C_{SS}) was lower than the observed maximum concentration (C_{max}) after the SI (1.70 ± 0.52 vs 3.82 ± 1.78 μg/ml)(Table 2 and Fig. 1). $T_{1/2_Z}$ and Cl were, respectively, longer and higher after the PI than after the SI ($P < 0.05$), whereas V_Z and V_{SS} were not significantly different (Table 2). Differences observed between the two methods used to calculate Cl were negligible (Table 2). No statistically significant differences in ICG clearance were found among the three sets of measurements (Table 3).

Discussion

Kinetics after Short Infusion

After a short infusion, bupivacaine kinetics are best described with a two-compartment open model. We observed a shorter terminal half-life ($T_{1/2_Z}$) in dogs than that reported in humans (11). Similar findings have been reported by Arthur et al. for dogs (12). In another study in dogs, Irestedt et al. (13), reported high values of Cl (24–29 ml·min^{-1}·kg^{-1}) similar to those of Arthur et al. Our Cl values are lower than those reported by these two studies. The different values reported in the three studies may be due to differences in experimental design. We measured arterial concentrations in serum, whereas Arthur et al. measured arterial concentrations in whole blood. Irestedt et al. studied their dogs during laparotomy under thiopental and N_2O anesthesia, and Cl was extrapolated from the hepatic extraction ratio measured during the first hour after bupivacaine injection, i.e., during the distribution phase into the liver (10). In that case, the concentration measured in hepatic veins would have to be much lower than expected if distribution into the liver was achieved. This increased difference in concentration between artery and hepatic vein would have led to an increased extraction ratio and, therefore, to an increased Cl. The present study, performed at least 10

Table 2. Pharmacokinetic Parameters Obtained in the Six Dogs after SI and PI*

Dog	Weight (kg)		$T_{1/2_z}$ (min)	Cl† $(ml \cdot min^{-1} \cdot kg^{-1})$	V_c (L/kg)	V_z (L/kg)	V_{ss} (L/kg)	C_{max} (μg/ml)	C_{ss} (μg/ml)
1	25	SI	52	7.3	0.114	0.547	0.259	5.39	—
		PI	146	2.4 (2.4)	0.100	0.516	0.317	—	2.08
2	16	SI	39	17.5	0.230	0.994	0.723	2.52	—
		PI	81	4.1 (3.5)	0.033	0.477	0.181	—	1.45
3	16	SI	71	10.7	0.278	1.101	0.692	3.30	—
		PI	262	3.5 (3.7)	0.062	1.336	0.404	—	1.35
4	23	SI	47	6.0	0.099	0.403	0.357	4.77	—
		PI	287	2.7 (2.6)	0.050	1.106	0.676	—	1.92
5	19	SI	43	9.3	0.175	0.573	0.456	3.94	—
		PI	124	5.4 (4.4)	0.175	0.954	0.665	—	1.14
6	27	SI	67	6.4	0.387	0.623	0.582	3.00	—
		PI	105	2.3 (2.2)	0.091	0.345	0.304	—	2.26
Mean	21	SI	53	9.5	0.214	0.707	0.512	3.82	—
		PI	167	3.4 (3.1)	0.085	0.789	0.424	—	1.70
SD	5	SI	13	4.5	0.109	0.276	0.188	1.78	—
		PI	86	1.2 (0.8)	0.051	0.399	0.203	—	0.52
			$P < 0.05$	$P < 0.05$	$P < 0.05$	NS‡	NS‡		

*Parameter abbreviations in text.

†The values in brackets were calculated as k_2/C_{ss}.

‡NS, not significant.

days after anesthesia, in dogs allowed to move, drink and eat normally, provides a more representative profile of bupivacaine kinetics in dogs, especially if compared with human values.

Kinetics after Prolonged Infusion

After a prolonged infusion, bupivacaine kinetics are best described with a two compartment open model. The coefficients of variation of the estimates of each parameter are reported in Table 1. The values reported for V_c are significantly higher for the PI group than for the SI group ($P < 0.05$). These differences should be interpreted with care, because curve fitting after the PI was done on concentration-time data with fewer multicompartmental characteristics than those obtained after the SI (10). Thus, a higher degree of uncertainty is associated with the estimates of parameters after the PI than after the SI. However, λ_Z also was calculated using log-linear regression of the observed terminal curve, without a change in values. In the same way, Cl also was calculated as the ratio of rate of infusion over C_{SS}, without a change in values (Table 2). Thus, $T_{1/2_Z}$, Cl and V_Z are more precisely known as V_c and V_{SS}.

After 24 hours of bupivacaine infusion, $T_{1/2_Z}$ showed a threefold increase when compared with the values observed after a short infusion. There are several possible explanations for this result; the prolongation in $T_{1/2_Z}$ could be related to inadequacy of modeling or to changes in kinetics induced by the PI. In the latter case, the increase in $T_{1/2_Z}$ may have been secondary to an increase in the volumes of distribution or to a decrease in hepatic clearance, the explanation we favor. A difference in the metabolism or in the protein binding of the two enantiomers of bupivacaine cannot be excluded as a cause of a decreased Cl (14).

It seems unlikely that the increase in $T_{1/2_Z}$ with the PI is due to inadequacy of the model used to describe kinetics with the occurrence of nonlinear kinetics.

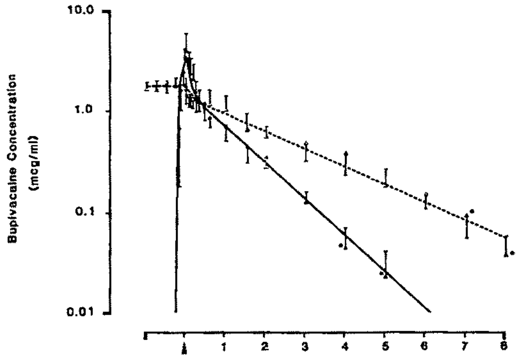

Figure 1. Serum concentration time course of bupivacaine in the six dogs studied after short infusion (SI) and prolonged infusion (PI). Each point represents the mean and standard deviation of the measured concentration and the lines the fitted curves. Solid triangles and line represents SI, open triangles and dotted line represents PI. *Bupivacaine was not detected in two dogs in both groups.

Steady state concentration after the PI was always below C_{max} after the SI (Table 1 and Fig. 1). In fact, prolongation in elimination would have appeared only if C_{SS} had been higher than C_{max} in case of zero-order kinetics (10).

The possibility that the increase in $T_{1/2_z}$ after the PI may have been related to the occurrence of a time-dependent volume of distribution (15) also seems unlikely. In fact, some time is required for distribution to be achieved and the increase in $T_{1/2_z}$ after the PI may be the result of more complete distribution after a longer period of time. In other words, drugs may penetrate a larger real volume of distribution upon PI. Apparent volume of distribution was similar after the SI and the PI, but this constancy in the apparent volume of distribution has to be interpreted with care as protein binding was not measured. We did not measure bupivacaine protein binding in serum because bupivacaine is known to be bound extensively to serum proteins, and any increase in free fraction would have increased Cl (10,16). Similarly, saturation in tissue binding seems unlikely, as this would have increased the free fraction and, consequently, Cl. This was not the case; Cl was found to be decreased after the PI.

We believe that the increase in $T_{1/2_z}$ after the PI is based on decreased Cl. Total body clearance was calculated by the mean of rate constants ($Cl = V_c(\lambda_1 \cdot \lambda_z)/k_{21}$), and as the ratio of rate of infusion over C_{SS} ($Cl = k_2/C_{SS}$). The values calculated by the two methods were similar (Table 2). This fact suggests that the model used to describe the time course of bupivacaine was adequate. Thus, the prolongation in $T_{1/2_z}$ after the PI when compared with the SI is due to a decrease in total body clearance. Because elimination of bupivacaine results only from hepatic metabolism (11), this is synonymous with hepatic clearance. Decreased hepatic clearance may be the result of decreased hepatic blood flow for drugs with high hepatic extraction ratios. Bupivacaine generally is reported to have a low hepatic extraction ratio; however, Irestedt et al. reported a high extraction ratio in their dogs (13). To eliminate the possibility that flow-dependent changes in Cl occurred in our experiment, we measured ICG clearance during the last hour of the PI (near steady-state), and 90 minutes after cessation of infusion after both the SI and the PI. The absence of change in ICG clearance during the postdistributive phase after the SI, and during both the steady-state period and 90 minutes after cessation of the PI rules out the possibility that a change in hepatic blood flow was the cause of the observed decrease in Cl.

Table 3. ICG Clearance Measured in the Six Dogs*

	SI (90 minutes)	PI (last hour)	PI (90 minutes)
Mean	30.3	30.4	28.0
SD	6.7	7.5	2.9

*In $ml \cdot min^{-1} \cdot Kg^{-1}$, ANOVA failed to demonstrate any significant difference.

Decreased hepatic clearance may also be the result of decreased intrinsic hepatic clearance. Moreover, intrinsic hepatic clearance of drugs with low hepatic extraction ratio depends both on free drug concentration and intrinsic clearance of free drug (Cl_I') (16). Bupivacaine has a relatively low hepatic extraction ratio of 0.38 in humans (11). Therefore, its clearance is more dependent on free (unbound to serum proteins) intrinsic hepatic clearance (Cl_I') and on the extent of protein binding than on liver blood flow (16). Bupivacaine is extensively bound to serum proteins (95% in humans), and only minor differences in binding between dogs and humans have been reported (17). Thus, we can assume that the observed decrease in Cl is only due to a decrease in Cl_I' because any decrease in free fraction would have led to an increase in Cl (16).

For these reasons, a decrease in intrinsic clearance of free bupivacaine appears to be the only explanation for the observed decrease in Cl. A similar decrease in Cl_I' has been reported after prolonged infusion of lidocaine both in dogs and humans (4,5). However, unlike bupivacaine, lidocaine has a relatively high hepatic extraction ratio (0.65) and, therefore, is considered to be flow-limited in its metabolism (11,16). Despite this kinetic profile, the decrease in lidocaine clearance observed in humans has been shown to be related to a decrease in intrinsic hepatic clearance, because: 1) indocyanine green clearance did not change in humans (4); and 2) competitive inhibition of metabolism due to stereo-occupancy of hepatic microsomes by lidocaine metabolites has been demonstrated in rats (18).

One additional explanation for the decrease in Cl after the PI, which was not addressed in this study, is related to the physical structure of bupivacaine, i.e., it is a mixture of two optical isomers. Differences in toxicity, and in the duration of action of the two isomers have been reported (19). These differences are thought to be a consequence of enantioselective differences in binding to α-1-acid glycoprotein (14,19). However, differences in Cl_I' of the two enantiomers cannot be excluded as an explanation of the changes in racemate kinetics observed with time.

In conclusion, after a prolonged infusion of bupivacaine, as compared with a short infusion in conscious dogs, we observed a prolongation in $T_{1/2_z}$. We believe that this is due to a decrease in intrinsic hepatic clearance. A similar change in bupivacaine kinetics after prolonged infusion may occur in humans. This study demonstrates that extrapolation of kinetic data obtained after a short infusion (or a bolus injection) of bupivacaine to prolonged infusion must be done with care.

The authors thank Dr. K. Samii and Dr. R. Mazze for their valuable review of the manuscript and Dr. J. F. Giudicelli for laboratory facilities.

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Supplemental Oxygen after Ambulatory Surgical Procedures

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MURRAY RS, RAEMER DB. MORRIS RW. Supplemental oxygen after ambulatory surgical procedures. Anesth Analg 1988;67:967–70.

The aim of this study was to determine the need for supplemental oxygen during recovery from general anesthesia for ambulatory surgery in healthy women without obesity or respiratory disease. Arterial oxygen saturation by pulse oximetry (Spo_2) was monitored throughout the first postoperative hour in 164 patients. The patients breathed room air during recovery. Supplemental oxygen was given only to those who became hypoxemic ($Spo_2 \leq 92\%$). It was discontinued at the end of 15 minutes and reinstituted for another 15 minutes if hypoxemia recurred. Twelve patients (7%) became hypoxemic and required supplemental oxygen for various periods of time up to 105 minutes. The need for supplemental oxygen increased with increasing age ($P < 0.05$) but was not associated with a history of cigarette smoking, tracheal intubation, amount of opioids or sedatives given intraoperatively, anesthetic duration, or level of consciousness during recovery. Hypoxemia was neither predictable nor clinically apparent. We recommend that, unless arterial oxygenation is monitored, ambulatory patients should routinely receive supplemental oxygen during recovery from general anesthesia.

Key Words: HYPOXIA—postoperative. OXYGEN—postoperative. ANESTHESIA—outpatient.

Hypoxemia is common in surgical inpatients breathing room air during recovery from general anesthesia (1). It is more likely with abdominal (2) or thoracic incisions (3), obesity (4), respiratory disease (5), or increased age (6). If oxygenation is not monitored, supplemental oxygen has been recommended for all patients after general anesthesia (7).

Ambulatory patients are less likely to have the above risk factors and have a lower prevalence of postoperative hypoxemia (8). Thus, routine supplemental oxygen may not be necessary after ambulatory surgery. Our aim in this study was to determine the need for supplemental oxygen after anesthesia for ambulatory surgery in healthy women without obesity or respiratory disease.

Methods

One hundred sixty-four women undergoing a variety of surgical procedures (mostly gynecological) under general anesthesia as ambulatory patients participated in this study. Prior institutional review approval and informed patient consent were obtained. All patients were ASA physical status I or II, 18 years or older, not obese (body mass index < 30 kg/m^2) (9) and without symptoms of pulmonary disease. As many patients as possible were enrolled and we studied those for whom an oximeter was available when they came to the recovery room. Three patients with problems requiring postoperative admission to the hospital or anesthetic complications were excluded from the study.

Preoperative assessment was made after the patient was placed on a stretcher but before administration of any medication. The patient's age and cigarette smoking history (in pack-years) were recorded. An Ohmeda Biox model 3700 pulse oximeter (Ohmeda, Boulder, CO) was used to measure the arterial oxygen saturation of hemoglobin (Spo_2). Postoperatively, use of tracheal intubation, duration of anesthesia, and types and amounts of opioids and sedatives used intraoperatively were recorded. The amounts of opioids and sedatives used classified as low (not exceeding 100 μg fentanyl or 2 mg midazolam) or high (more than 100 μg fentanyl or 2 mg midazolam).

Arterial oxygen saturation of hemoglobin was continuously monitored for one hour after the patient arrived in the recovery room. The patient breathed room air during recovery, unless the Spo_2 decreased

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Received from the Department of Anesthesia, Brigham and Women's Hospital, Boston, Massachusetts. Accepted for publication May 4, 1988.

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Table 1. Potential Risk Factors of the Patients Who Required Supplemental Oxygen

Age (years)	Smoking history (pack-years)	Preoperative Spo$_2$ (%)	Anesthetic duration (minutes)	Lowest Spo$_2$ (%)	Time of onset of hypoxemia (minutes)	Duration of need for Supplemental oxygen (minutes)
32	15	97	30	91	0	15
33	8	99	170	83	0	30
34	0	98	30	80	8	7
37	10	96	25	91	3	12
39	0	98	35	89	0	30
41	20	99	40	90	1	14
43	36	95	40	91	0	60
44	0	98	40	91	0	15
51	0	98	15	91	32	13
53	40	96	20	90	6	24
62	50	96	75	89	0	45
72	0	96	100	89	0	105

to 92%, the level we used to define hypoxemia. When a patient became hypoxemic, the investigators instituted supplemental oxygen, which was given through a disposable plastic face mask with flows of at least 6 L/min. At the end of each 15-minute period, measured from arrival in the recovery room, those patients receiving supplemental oxygen were allowed to breath room air. Supplemental oxygen was readministered if hypoxemia with air breathing recurred. Arterial oxygen saturation of hemoglobin was monitored for at least 30 minutes after removal of supplemental oxygen. The times at which hypoxemia occurred and after which supplemental oxygen was no longer required were recorded.

On arrival in the recovery room and at each hypoxemic incident, the conscious state was assessed, using the stimulation required for eye opening from the Glasgow Coma Scale, i.e., eyes open spontaneously, in response to oral commands or pain, or not at all (10).

The association between each of the potential risk factors and the number of patients requiring supplemental oxygen was analyzed. For attribute data, Fisher's exact test (11) was used and for continuous data the Wilcoxon's rank sum test was used to calculate the probability that the proportions did not differ; $P < 0.05$ was considered statistically significant.

Results

Preoperative Spo$_2$ levels were $\geq$ 95% in all patients. Postoperatively, 12 (7%) of the 164 patients had Spo$_2$ $\leq$ 92% and so were given supplemental oxygen (Table 1). Seven patients (4%) had readings $\leq$ 90%; the lowest Spo$_2$ was 80%. In no case was there clinically evident respiratory depression or obstruction, nor were there signs of hypoxemia (e.g., cyanosis or tachypnea). The onset of hypoxemia was within 3 minutes of arrival in the recovery room in nine patients, and between 3–10 minutes in two patients but occurred at 32 minutes in one patient. One patient became hypoxemic two minutes after receiving meperidine, 75 mg, intramuscularly; this was the only instance of postoperative opioid administration preceding hypoxemia. No hypoxemia occurred after patients had recovered sufficiently to move from the stretcher to a chair.

Supplemental oxygen increased Spo$_2$ to $\geq$ 95% within 2 minutes and maintained these levels in all cases. It was required for varying times (Table 1); four patients needed supplemental oxygen after 30 minutes.

The need for supplemental oxygen increased significantly with increasing age (Table 2). There was no statistically significant association between the requirement for supplemental oxygen and history of cigarette smoking, tracheal intubation, amounts of opioids and sedatives used, duration of anesthesia, or levels of consciousness during recovery (Table 2).

Discussion

Hypoxemia in the early postoperative period can result from alveolar hypoventilation, ventilation–perfusion abnormalities, desaturation of venous blood (from depressed cardiac output or increased oxygen consumption), or diffusion hypoxia (12). Hypoxemia disappears rapidly in patients who do not have

Table 2. Associations between Potential Risk Factors and Patients Who Required Supplemental Oxygen

	Number of patients requiring supplemental oxygen	Number of patients not requiring supplemental oxygen	Fisher's exact test (*P*)
Attribute data			
Tracheal intubation			
Not intubated	2	58	0.14
Intubated	10	94	
Amounts of opioids and sedatives			
Low dose	10	128	0.94
High dose	2	24	
Level of consciousness			
Eyes open spontaneously	3	59	0.29
Eyes open in response to verbal command	7	88	
Eyes open in response to pain	1	3	
	Patients requiring supplemental oxygen	Patients not requiring supplemental oxygen	Wilcoxon's rank sum test (*P*)
Continuous data	Median	Median	
Age (years)	42	36	0.01
Smoking history (pack-years)	9	2	0.08
Duration of anesthesia (minutes)	38	30	0.24

abdominal or thoracic incisions (7) or pulmonary impairment (13).

Ambulatory patients are generally healthy, and, not having had thoracic or major abdominal surgery, would not be expected to have a high prevalence of hypoxemia during recovery from general anesthesia. Intermittent measurements of postoperative Spo_2 during routine recovery room care have confirmed this, with $Spo_2 \leq 90\%$ in 14% of inpatients but only 1% of ambulatory patients (8).

Although our results suggest that most women without pulmonary disease or obesity do not require supplemental oxygen after general anesthesia for ambulatory surgery, desaturation does occur in some. This is neither predictable from the factors we recorded nor clinically apparent. It is not surprising that we did not detect hypoxemia clinically as alveolar hypoventilation is not the usual cause of postoperative hypoxemia (14), and the degree of hypoxemia we encountered is not severe enough to cause obvious clinical signs (15).

We were intentionally conservative in choosing $Spo_2 \leq 92\%$ as our definition of hypoxemia. Some have defined hypoxemia as a $Spo_2 \leq 90\%$; this would have reduced both the number of patients requiring supplemental oxygen and the duration of oxygen administration. Hypoxemia was not predictable from the factors we recorded in the seven patients with $Spo_2 \leq 90\%$.

The association between increased age and postoperative hypoxemia confirms previous reports. Kitamura et al. found the decrease in Pao_2 below preoperative levels 1–2 hours postoperatively to be greater in older patients. Anesthesia causes a greater reduction in functional residual capacity (FRC) (16) and increased ventilation–perfusion inequality with increased age (6).

No simple recommendations can be made, on the basis of the present data, for how long supplemental oxygen should be given to healthy outpatient women recovering from general anesthesia. No patient needed supplemental oxygen after moving from the stretcher to a chair. Fairley (7) suggests that oxygen should be given until patients are fully awake. Although awake patients may have higher saturations, we could not show this.

Brief periods of moderate hypoxemia may not be harmful to healthy people and it could be argued that none of these patients needed supplemental oxygen during their recovery. However, moderate hypoxemia may precede the occasional severe episode and it seems prudent to maintain high levels of Spo_2. Because modest increases in inspired oxygen concentration are considered safe (17) and were effective, we conclude that supplemental oxygen should be given to all ambulatory patients recovering from general anesthesia.

We thank the patients for participating in this study, the nursing staff of the Day Surgery Unit, David E. Leith, MD, Diane Warren, BS, and Ms. Alyce Bruce.

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Sixty-Two Years Ago In
Anesthesia & Analgesia

Henry I. Dorr, MD, DDS, SCD: Signally honored by the Associated Anesthetists and the IARS. Current Researches in Anesthesia & Analgesia 1926;5:48–50.

Who was Henry I. Dorr? He was a visionary. What did he do in anesthesiology? He provided one of the cornerstones for the development of academic anesthesia: the first endowed chair in anesthesia. Born to a New England farming family on December 28, 1844, just a short time before Morton introduced the world to ether anesthesia at the Massachusetts General Hospital, Dorr's childhood was not a happy one. So unhappy, in fact, that at age 8 he ran away from home, broke except for being "commander in chief of five red cents, earned honestly." Life was no less difficult away from home. In 1861 life became dangerous as well as difficult when he joined the Union Army for the duration of the Civil War. Three horses were shot from under him—he nevertheless survived unscathed. In 1869 and 1870 he studied at Harvard, and in 1876 he graduated from the Philadelphia Dental College. Dorr continued at the P.D.C. for the next 20 years, eventually becoming not only professor but trustee and financial head of P.D.C. While thus occupied, Dorr even managed to study medicine at Jefferson Medical College, where he received his M.D. in 1883. It was while at P.D.C. and Hahnemann that Dorr became so interested in anesthesia that he endowed a chair Harvard—not a chair in anesthesia, but a chair for research in anesthesia. It was not until 1941 that Henry K. Beecher, Anaesthetist in Chief at the MGH, was appointed Henry Isaiah Dorr Professor of Research in Anaesthesia, the first appointment to the first endowed chair in anesthesia in the world. Beecher went on to become one of the founders of modern academic anesthesiology. When he retired in 1970, Richard J. Kitz was appointed the second Henry Isaiah Dorr Professor of Research in Anesthesia, thus assuring continuation of the standards of academic excellence established by Beecher.

Ventilatory Effects of Continuous Epidural Infusion of Fentanyl

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RENAUD B. BRICHANT JF, CLERGUE F, CHAUVIN M, LEVRON JC, VIARS P. Ventilatory effects of continuous epidural infusion of fentanyl. Anesth Analg 1988;67:971–5.

The effects of a continuous epidural administration of fentanyl on pain and on ventilation were studied in eight patients scheduled for orthopedic surgery of the knee. In each subject, epidural fentanyl was given by a bolus dose of 1 $\mu g \cdot kg^{-1}$, followed by a continuous infusion of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ over 18 hours. Ventilatory measurements were performed during quiet breathing and during CO_2 stimulation tests before surgery. After surgery measurements were made before epidural administration of fentanyl; 1, 2, 5, 18 hours after the start of epidural fentanyl infusion; and 6 hours after its discontinuation. Adequate pain relief was achieved in all patients during fentanyl administration. No significant change in ventilation was noted during quiet breathing. The slope of the ventilatory response to CO_2 ($\dot{V}E/PaCO_2$) decreased significantly from 1.46 ± 0.2 to 0.75 ± 0.1 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ (mean ± SEM; $P < 0.05$) one hour after the onset of fentanyl administration, and remained stable throughout the infusion. Eighteen hours after the onset of epidural fentanyl infusion, $\dot{V}E/PaCO_2$ was still 0.76 ± 0.14 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$. At the end of fentanyl administration, plasma fentanyl levels measured in six patients had progressively increased from 0.42 ± 0.02 ng·ml one hour after the onset of the infusion to 1.54 ± 0.19 ng·ml at the end of the infusion. These results suggest that a continuous epidural administration of fentanyl is a technique of analgesia that can provide adequate pain relief but which is associated with ventilatory depression. However, with the doses used in this study, the ventilatory depression remained moderate and of no demonstrable clinical consequence.

Key Words: ANALGESICS—fentanyl. ANESTHETIC TECHNIQUES—epidural, fentanyl. PAIN—postoperative. VENTILATION—carbon dioxide response.

Epidural administration of morphine has been shown to produce profound and long-lasting analgesia (1). However, various undesirable side effects are associated with epidural morphine analgesia, among which the most serious is biphasic respiratory depression (2). The early respiratory depression is thought to be related to the vascular uptake of the narcotic, whereas the delayed depression seems to result from a cephalad movement of morphine into the cerebrospinal fluid (CSF), with consequent depression of respiratory centers (3). The risk of delayed respiratory depression explains anesthesiologists' frequent reluctance to use epidural narcotics for postoperative analgesia.

It has been suggested that lipid-soluble narcotics such as fentanyl, because of their short transit times in the CSF, are less likely to be associated with delayed respiratory depression (4). However, analgesia produced by an epidural bolus of fentanyl is of short duration (5,6). Therefore, a continuous epidural infusion of fentanyl would be more suitable for postoperative analgesia. However, the respiratory consequences of this technique have not previously been determined.

The present study was therefore conducted to examine the effects of continuous epidural administration of fentanyl on: 1) pain relief, 2) ventilatory variables during quiet breathing and CO_2 stimulation tests, and 3) plasma fentanyl levels.

Materials and Methods

Subjects

After giving written, informed consent to the institutionally approved protocol, eight patients scheduled for orthopedic surgery of the knee (ligamentoplasty)

Received from the Département d'Anesthésie-Réanimation, Groupe Hospitalier Pitie-Salpetriere, Paris, France, and the Département d'Anesthésie-Réanimation Hôpital Ambroise Pare, Boulogne, France. Accepted for publication May 4, 1988.

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participated in the study. Mean age was 32 years (range, 21–40 years). Mean weight was 65 kg (range, 45–85 kg). No patient had clinical evidence of heart or pulmonary disease.

Ventilatory Measurements

Ventilatory measurements consisted of minute ventilation ($\dot{V}_E$), tidal volume (V_T), respiratory frequency (f), and end-tidal P_{CO_2} (Pa_{CO_2}) when breathing room air and during a CO_2 stimulation test (method of Read) (7). For preoperative baseline measurements, each patient took two rebreathing tests: the first was regarded as practice; the second was compared with the six postoperative tests and was considered the baseline measurement. All the patients were studied in a supine, 30° head up position before and after surgery.

The subjects, with a noseclip in place, breathed through a mouthpiece connected to a #2 Fleisch pneumotachograph measuring inspiratory and expiratory flows. Inspiratory and expiratory lines were separated by a Mauve and Lagarde one-way valve. The dead space of the circuit was 75 ml. The resistances of the inspiratory and expiratory lines were, respectively, 2.4 and 3.5 cm $H_2O \cdot L \cdot sec^{-1}$ at a flow of 1 L·sec. Volume was measured by electronically integrating the flow signal obtained from the pneumotachograph connected to a Godart 17212 differential pressure transducer (Bilthoven, Holland). The use of a circuit with a relatively high dead space resulted in somewhat high values of pulmonary ventilation. End-tidal P_{CO_2} was measured with a Hewlett-Packard 47210 A capnometer calibrated before and after each measurement with two different gases. All signals were recorded on an FM magnetic tape recorder (Hewlett-Packard 3964 A) and displayed on a computer (Hewlett-Packard).

Times of inspiratory (T_I), expiratory (T_E) and total breathing cycles (T_{TOT}) were measured from the flow signal. Tidal volume was measured by integrating the flow signal. Respiratory frequency and minute ventilation were calculated from these values. For the rebreathing tests, linear regression equations were calculated by plotting $\dot{V}_E$ against end-tidal P_{CO_2}. Results are expressed by the slope ($\dot{V}_E/Pa_{CO_2}$) and the position of the curve at 55 mm Hg ($\dot{V}_E^{55}$). All values of volume and flow are expressed in BTPS.

Procedure

Baseline ventilatory measurements were performed the day before surgery. After insertion of an epidural catheter at the L2–3 interspace, operative anesthesia was induced with reinjection of standard doses of bupivacaine through the catheter. No respiratory depressants were administered. As soon as the patients complained of postoperative pain (at least 150 minutes after the last injection of bupivacaine), fentanyl was administered epidurally: a bolus of 1 μg/kg followed by a continuous infusion of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ over a period of 18 hours.

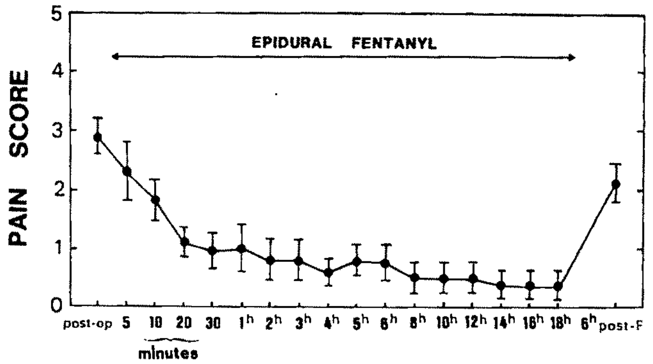

Figure 1. Mean values (± SEM) of the pain score before (postop), during, and six hours after discontinuation of the infusion of epidural fentanyl (6 h post-F).

Ventilatory measurements were repeated before the fentanyl injection, at 1, 2, 5, and 18 hours after the start of fentanyl administration, and 6 hours after the end of fentanyl infusion.

Pain was scored before each blood sampling on a grading scale from 0 to 5: 0 = no pain; 1 = very mild pain discerned as discomfort rather than actual pain; 2 = moderate pain that could remain forgotten for long periods; 3 = moderate but persistent pain; 4 = severe pain with urgent demand for analgesics; 5 = unbearable pain with distress state.

Blood samples were collected at 5, 10, 20, and 30 minutes and then at 1, 2, 3, 5, 7, 9, 15, and 18 hours after the start of epidural fentanyl injection, and 6 hours after its discontinuation. Samples were immediately centrifuged and the plasma fractions stored at −20°C. In six patients, plasma concentrations of fentanyl were measured in duplicate by radioimmunoassay (8). For technical reasons, plasma fentanyl concentrations were not measured in the first two patients. The precision of these measurements was 99.8 ± 0.81% with a coefficient of variation of 1.56 ± 1.51% (SD), over the range 0.05–2 ng/ml.

Data are expressed as mean ± SEM. Ventilatory variables were analyzed with a two-way analysis of variance *t*-tests corrected for multiple comparisons, while pain score data were compared using a Friedman analysis of variance by ranks; $P < 0.05$ indicated significance.

Table 1. Ventilatory Variables during and Six Hours after Discontinuation of the Continuous Epidural Infusion of Fentanyl*

	Control	1 hour	2 hours	5 hours	18 hours	6 hours after discontinuation
$\dot{V}_E$ (L/min)	11.3 ± 0.8	10.5 ± 0.8	10.0 ± 0.7	9.7 ± 0.8	11.3 ± 0.5	11.9 ± 1.2
f (beats/min)	18.2 ± 1.0	19.4 ± 2.7	20.4 ± 1.7	18.5 ± 1.4	18.2 ± 1.4	20.5 ± 1.5
V_T (ml)	603 ± 51	634 ± 81	541 ± 54	572 ± 53	556 ± 28	484 ± 35
$Paco_2$ (mm Hg)	37.2 ± 1.7	39.4 ± 1.8	41.0 ± 2.2	42.6 ± 2.1	42.6 ± 2.1	38.4 ± 2.1

*All values are mean ± SEM; $n = 8$.
Comparison with control value: †$P < 0.05$; ‡$P < 0.001$; §$P < 0.001$ v control.

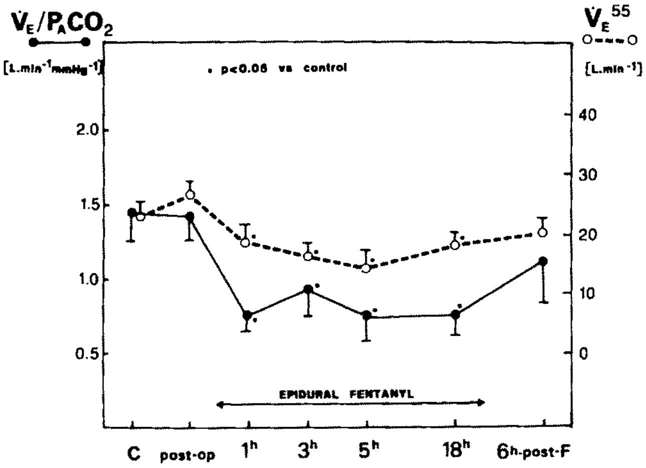

Figure 2. Mean values (± SEM) of the slope of the ventilatory response to CO_2 ($\dot{V}_E/Paco_2$), and of minute-ventilation at a $Paco_2$ of 55 mm Hg ($\dot{V}_E^{55}$), the day before surgery (C), after surgery (postop), during the infusion of epidural fentanyl, and after its discontinuation (6 h post-F).

Results

The results of the mean pain scores are shown in Figure 1. The onset of pain relief was rapid, and the mean pain score decreased significantly after fentanyl administration ($P < 0.001$): from 2.9 ± 0.3, before fentanyl administration, to 1.8 ± 0.3 at 10 minutes, to 1.1 ± 0.3 at 15 minutes and to 0.9 ± 0.3 at 30 minutes. Fifteen minutes after the onset of fentanyl administration, all subjects had a pain score of 2 or lower. During the 18-hour period of the study, adequate pain relief was achieved, with mean pain scores remaining lower than 1 throughout the 18-hour fentanyl infusion. None of the patients required other analgesics during the study. Six hours after the end of fentanyl infusion, the mean pain score returned to 2.1 ± 0.3.

The results of the ventilatory variables during fentanyl infusion are shown in Table 1 and in Figure 2. No change in the ventilatory variables was observed between control preoperative measurements and postoperative measurements performed before fentanyl administration. The decrease in resting minute ventilation and the increase in P^Aco_2 during fentanyl administration were not statistically significant. Respiratory frequency and tidal volume remained unchanged throughout the study. None of the patients developed clinically evident respiratory depression. However, the ventilatory response to CO_2, as assessed by the slope $\dot{V}_E/Paco_2$, and minute ventilation at a $Paco_2$ of 55 mm Hg, remained significantly decreased throughout the study period.

Plasma fentanyl levels are shown in Figure 3. Mean plasma concentrations of fentanyl increased rapidly between the onset of the administration and the fifth hour: 0.42 ± 0.02 ng/ml at 1 hour, 0.68 ± 0.07 ng/ml at 2 hours, 0.95 ± 0.20 ng/ml at 5 hours. Thereafter, the increase in plasma values was slower, until the end of the infusion: 1.21 ± 0.20 ng/ml at 15 hours and 1.54 ± 0.19 ng/ml at 18 hours. Only one patient had a plasma level higher than 2 ng/ml at the end of the infusion (2.05 ng/ml in patient 6). Six hours after the end of fentanyl administration, mean plasma values were 0.93 ± 0.26 ng/ml. Two patients had a slow elimination rate, with plasma levels of fentanyl still at 1.66 ng/ml and 1.46 ng/ml.

Discussion

Cousins and Mather (1) have reported that the use of epidural morphine for postoperative pain relief is limited by several factors: its onset of action requires more than 35 minutes, it is difficult to titrate the dose requirement, and the peak of the respiratory depression may be delayed (2). In contrast, lipophilic narcotics, such as fentanyl, may possess a better efficacy/safety ratio (1), and have been shown to be effective for postoperative pain relief (5,6,9). The present study confirms that continuous epidural fentanyl can provide satisfactory pain relief after orthopedic surgery. Most patients in this study had complete pain relief. The onset of analgesia was obtained within 20 minutes in all patients. Thus, even if complete pain relief is not achieved with an initial infusion rate of epidural fentanyl, the rate of administration can be increased more rapidly than with epidural morphine.

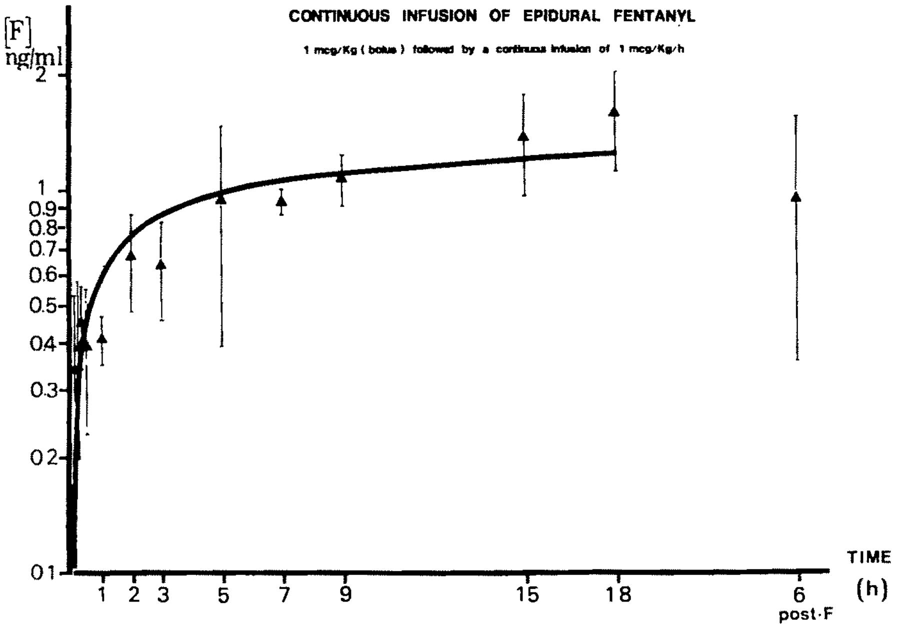

Figure 3. Mean values (± SEM) of plasma concentrations of fentanyl during and six hours after discontinuation of the epidural infusion of fentanyl.

This increase in the infusion rate, however, will be limited; once effective intensities of epidural fentanyl analgesia have been reached, little therapeutic benefit can be obtained from further increasing the dose of fentanyl (1). This has also been our clinical experience when using this technique of analgesia for intense postoperative pain.

This study also demonstrates that the administration of fentanyl by the epidural route is associated with ventilatory depression. Lam et al. (10) observed no change in resting ventilation or in the CO_2 response after 100 μg of epidural fentanyl. In the present study, a statistically significant decrease in the ventilatory response to CO_2 was found after continuous epidural fentanyl, although the changes observed during resting ventilation remained moderate and insignificant. This study confirms the findings of Negre et al. (11), who observed a significant decrease in the CO_2 response after a single epidural administration of 200 μg of fentanyl. The magnitude of the ventilatory depression observed in the present study, a 38% decrease in the CO_2 response slope, is similar to the ventilatory depression usually associated with parenteral narcotics commonly administered during the postoperative period. Weil et al. noted a 42% decrease in the mean CO_2 response slope 75 minutes after a subcutaneous administration of 7.5 mg of morphine (12). Engineer and Jennett observed a 53% decrease in the CO_2 response slope after 75 mg of IV meperidine (13). Negre et al. noted a 23% decrease in the mean CO_2 response slope 30 minutes after 200 μg of IM fentanyl (11).

This study also shows that the decrease in the ventilatory response to CO_2 associated with epidural infusion of fentanyl appears rapidly but remains stable throughout the epidural infusion. None of the patients in this study developed a clinically significant respiratory depression. To our knowledge, the epidural administration of a lipid-soluble narcotic, such as fentanyl or meperidine, has not yet been reported to have been associated with delayed ventilatory depression. Recently, Rawal et al. reported that the 13 cases of delayed ventilatory depression, out of over 14,000 patients who received epidural narcotics, were observed only in patients given epidural morphine (14). Therefore, it seems that continuous administration of epidural fentanyl does not cause greater respiratory depression than parenteral narcotics, when administered in appropriate doses. The absence of delayed ventilatory depression could make ventilatory monitoring of these patients easier, as it is after parenteral narcotics.

The mechanism of ventilatory depression after epidural narcotics are not yet clearly understood. In this study, 5 hours after the onset of epidural infusion, we observed a 38% decrease in the mean CO_2 response slope that corresponded to a mean plasma fentanyl level of 0.95 ± 0.20 ng/ml. In a previous study, Cartwright et al. reported that a 50% depression of the CO_2 response slope corresponded to plasma fentanyl levels in the range of 1.5–3.0 ng/ml (15). Therefore, our findings suggest that ventilatory depression, as observed in the present study, results mainly from vascular absorption via the epidural veins. However, the rapid development of ventilatory depression, seen 1 hour after the onset of the epidural infusion and associated with mean plasma fentanyl concentrations lower than 0.5 ng/ml does not exclude other explanations for this ventilatory depression, such as a rostral spread of the narcotic in the CSF, or a redirection of blood flow through vertebral veins to the brain (1).

Despite a progressive increase in plasma fentanyl concentrations, the ventilatory depression remained unchanged during fentanyl infusion. The main explanation for this is probably that the end of the infusion corresponded in all patients to the morning after the day of surgery. At that time, the various activities surrounding the patient probably played a role in this phenomenon. Other mechanisms, however, such as a tolerance to the effect of narcotics, cannot be excluded, as shown in some recent studies (16).

This study shows that epidural fentanyl, administered by a continuous infusion, can provide an efficient postoperative analgesia and is responsible for a moderate ventilatory depression. Further studies are now needed to determine whether patients receiving lipid-soluble narcotics epidurally require monitoring different from that necessary for patients given IM morphine or meperidine during the postoperative period.

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1988;67:976–81

Cerebrospinal Fluid Concentrations of Substance P and (Met)Enkephalin-ARG^6-PHE^7 during Surgery and Patient-controlled Analgesia

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SJÖSTRÖM S, TAMSEN A, HARTVIG P, FOLKESSON R, TERENIUS L. Cerebrospinal fluid concentrations of substance P and (met)enkephalin-Arg^6-Phe^7 during surgery and patient-controlled analgesia. Anesth Analg 1988;67:976–81.

The possible role of two neuropeptides (substance P and (Met)enkephalin-Arg^6-Phe^7) in nociception were studied in 14 surgical patients. Lumbar cerebrospinal fluid (CSF) concentrations of the putative excitatory afferent transmitter substance P and the μ and δ receptor agonist (Met)enkephalin-Arg^6-Phe^7 were measured during general anesthesia for abdominal surgery and during the postoperative period when patient-controlled analgesia (PCA) was used for control of pain. The CSF was sampled through an intrathecal catheter. Seven of the patients were randomly assigned to receive neurolept anesthesia; the rest were given isoflurane anesthesia without narcotics. No statistically significant changes occurred in substance P concentrations in CSF during surgery or postoperative PCA, nor were there significant differences between the two groups. There was, however, a significant correlation between CSF substance P concentrations before the start of PCA and pain assessment on a visual analogue scale. The individual changes in substance P concentrations during PCA was also inversely correlated to the consumption of meperidine. The CSF (Met)enkephalin-Arg^6-Phe^7 concentrations were below the level of detection in seven of the patients before anesthesia. A large interindividual variability in both substance P and (Met)enkephalin-Arg^6-Phe^7 concentrations was evident. The absence of major changes in CSF neuropeptide concentrations was unexpected. Apparently interindividual variations in neuropeptide output are considerable.

Key Words: PAIN, POSTOPERATIVE. SPINAL CORD, CEREBROSPINAL FLUID. POLYPEPTIDES, SUBSTANCE P, (MET)ENKEPHALIN.

Substance P has been suggested as a neurotransmitter in primary, nociceptive afferents terminating in laminae II and III in the spinal dorsal horn (1,2). The release of substance P from primary afferents is said to be modulated by descending and local pain inhibitory systems (3) with transmitters such as norepinephrine, acetylcholine, enkephalin, and serotonin (4–7). Changes in pain perception induced by injury or after drug-induced pain relief might affect the spinal release of substance P. Conversely, activity of substance P releasing neurons and enkephalin containing interneurons might influence individual pain perception and responsiveness to opioid analgesia in acute pain states (8–10). Little information is available in the literature regarding the fluctuations in cerebrospinal fluid (CSF) levels of neuropeptides over time. In the present study, lumbar concentrations of substance P and one of the enkephalins, (Met)enkephalin-Arg^6-Phe^7 in CSF were measured in surgical patients during the preoperative period, during general anesthesia and surgery, and during the postoperative period when patient-controlled analgesia (PCA) was used for pain relief. We investigated two groups of patients subjected to similar surgical procedures but different anesthetic protocols.

Supported by grants from the Bank of Sweden Tercentenary Foundation, 81/120, and the Swedish Medical Research Council, 5095.

Received from the Departments of Anesthesiology and Hospital Pharmacy, University Hospital, Uppsala and Department of Pharmacology, University of Uppsala, Sweden. Accepted for publication May 13, 1988.

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Methods and Materials

This study was approved by the Ethics Committee of the Medical Faculty of Uppsala University.

Patients

Fourteen patients (four men and ten women) scheduled for surgery gave their informed consent to participate in the study. The mean age was 36 ± 12 years (mean ± standard deviation) and the height averaged 1.70 ± 0.08 m. Most of the patients suffered from inflammatory bowel diseases. None of the patients had any symptoms or signs of psychic disease, renal or hepatic dysfunction, or any history of drug or alcohol abuse.

Anesthesia

The patients were randomized into two groups, one designated the opioid group and the other the non-opioid group. The anesthetic procedure differed between the groups, but the patients were otherwise treated similarly. All patients were premedicated with oral 100-mg pentobarbital approximately 1.5 hours before induction of anesthesia.

In the opioid group, anesthesia was induced with thiopental plus a single 5-mg dose of droperidol. Orotracheal intubation was performed after 0.1 $mg \cdot kg^{-1}$ pancuronium bromide. Anesthesia was maintained with nitrous oxide and oxygen 70:30 and 0.1 to 0.2 mg increments of fentanyl citrate as required. Additional 1- to 2-mg increments of pancuronium were given as needed. In the non-opioid group, anesthesia was also induced with thiopental and a single dose of 5-mg droperidol and orotracheal intubation was performed after 0.1 $mg \cdot kg^{-1}$ pancuronium bromide. During surgery anesthesia was maintained with nitrous oxide and oxygen 70:30 and isoflurane and pancuronium as needed.

Postoperatively, the muscle relaxation was reversed. After tracheal extubation, the patients were transferred to a recovery room, where they remained overnight. Cuff blood pressure and respiratory rate were checked at least hourly. Blood transfusions and intravenous fluids were given in accordance with the clinical requirements of each patient.

Patient-controlled Analgesia

When the patients required pain relief, a programmable patient-controlled analgesia (PCA) pump (Prominject™) was connected to an intravenous cannula. The pump was programmed to deliver incremental 25-mg doses of meperidine with a minimum time interval between top-up doses of 15 min. The PCA continued until the morning of the day after the operation. The hourly consumption of meperidine was recorded.

Pain Assessment

Pain was assessed by means of a visual analogue scale (VAS) consisting of a 100-mm horizontal line marked "No pain" at its left end and "Worst imaginable pain" at its right end. The patients were not shown their previous ratings. Pain was assessed before the start of PCA, 4 hours after the start, and in the morning of the day after the operation.

CSF Sampling

Before induction of anesthesia, a thin (18-G) epidural Tuohy needle was introduced through a skin wheal of lidocaine and advanced between the second and third lumbar vertebra to the subarachnoid space. With the bevel of the needle directed cranially, a thin (18-G) catheter was introduced into the subarachnoid space, and advanced 5 to 6 cm beyond the tip of the needle. The catheter was subsequently used for the collection of CSF samples.

Samples of 2-ml of CSF were collected at the following times:

1. Immediately after the placement of the sampling catheter, and 30 minutes later, with the patient still awake (mean preoperative value is given).
2. Ten minutes after orotracheal intubation.
3. Ten minutes after the start of the operation.
4. Seventy minutes after the start of the operation.
5. Thirty minutes after extubation.
6. Immediately before the start of PCA.
7. Four hours after the start of PCA.

The sampling catheter was left in the subarachnoid space for a maximum period of 12 hours.

The CSF samples were mixed with EDTA (0.38 mol/l) 0.05 ml and immediately frozen at −70°C until analysis.

Analysis of Substance P and (Met)enkephalin-Arg^6-Phe^7

The CSF samples were fractionated on disposable hydrophobic columns (Sep-Pac, Waters). Samples (2 ml) were diluted with an equal volume of 0.1 M Na-phosphate buffer (pH 7.4) and the peptides were eluted in methanol: 0.1% trifluoroacetic acid in water (4:1 [vol/vol]).

Measurement of substance P immunoreactivity was done with radioimmunoassay (11). Cross-reaction of the substance P antiserum with the substance P (3-11) and (4-11) fragments was greater than 100%, with the (5-11) fragment 60% and the (6-11) fragment 20%. Cross-reaction with shorter C-terminal substance P fragments and N-terminal fragments (1-7) and (1-10) was less than 0.1%. The cross-reaction was less than 0.1% with enkephalins, somatostatin, eledoisin, or with beta-endorphin. The limit of detection was 1 fmol·ml^{-1}. The intra-assay variation and inter-assay variation were 4% and 11%, respectively, when determined at 20% displacement. Determination of (Met)enkephalin-Arg^{6}Phe^7 was also done with radioimmunoassay (12). The antibodies cross-react with peptide E, which contains the heptapeptide at the C-terminus, but show negligible cross-reaction with the enkephalins, (Met)enkephalin-Arg^6 or -Lys^6, corresponding (Leu)enkephalin hexapeptides and beta-endorphin. The limit of detection was 15 fmol·ml^{-1}. The intra-assay and inter-assay variation determined at 20% displacement was 2% and 12%, respectively.

Statistics

Results are given as mean ± SD in the text and tables and mean ± SEM in the figures. Wilcoxon's rank sum test or signed rank test were used to compare the groups and changes within the groups, respectively. The coefficient of determination (r^2) in the linear regression indicates the fraction of variance of the Y-values, which is accounted for by the variable *X*. $P < 0.05$ is considered to represent statistical significance.

Results

Clinical Course

The clinical course was uncomplicated in all but one patient (No. 2) in the opioid group, a patient reoperated upon because of hemorrhage about 12 h after the first operation. There was no significant difference between the opioid and the non-opioid groups with respect to age, body height, duration of operation, duration of anesthesia, or perioperative blood loss.

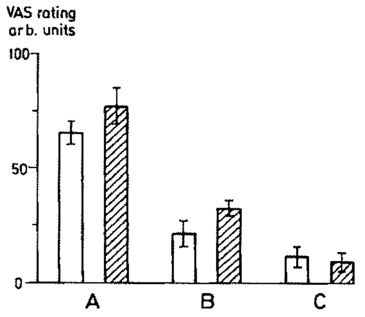

Figure 1. Pain assessments on the visual analogue scale (VAS) (A) before patient-controlled analgesia (PCA), (B) after a 4-h period of PCA, and (C) in the morning the day following operation. Zero arbitrary units represent "no pain," 100 arbitrary units "worst imaginable pain." Open bars represent the opioid group, hatched bars represent the non-opioid group.

PCA Consumption and Pain Assessment

All patients were satisfied with the pain relief from I.V. PCA. The meperidine consumption was 25.2 ± 12.1 mg·h^{-1} in the opioid group and 30.2 ± 14.4 mg·h^{-1} in the non-opioid group. The difference is not significant (n.s.). Pain assessment was not significantly different at any time between the groups (Fig. 1).

CSF (Met)enkephalin-Arg^6-Phe^7 and Substance P Concentrations

The concentrations of (Met)enkephalin-Arg^6-Phe^7 were below the limit of detection in 7 of the 14 patients before the operation (Table 1). The preanesthetic levels of substance P averaged 10.6 ± 5.0 fmol·ml^{-1} in the opioid group and 11.1 ± 3.1 fmol·ml^{-1} in the non-opioid group (n.s.) (Table 2). There was no correlation between the patients' sex, age, height, or meperidine consumption during PCA and the preanesthetic concentration of substance P.

No significant changes occurred in substance P concentrations during surgery or during PCA, nor were there any significant differences between the groups. A significant correlation existed between CSF substance P concentrations at the time of maximal pain, i.e., immediately before the start of PCA, and the pain assessment on the visual analogue scale (Fig. 2). The individual changes in substance P concentrations during PCA was inversely correlated to the consumption of meperidine (Fig. 3).

Discussion

It is widely accepted that anesthetic techniques influence postoperative pain suffering and analgesic re-

Table 1. (Met)Enkephalin-Arg^6-Phe^7 Levels in fmol·ml^{-1} during the Study Period

Pat. no.	1	2	3	4	5	6	7
Opioid group							
1	<	<	<	16	<	<	—
2	22	20	25	25	30	50	—
3	<	<	<	<	<	<	<
4	24	40	30	28	216	90	108
5	21	<	<	<	<	<	<
6	<	<	<	<	—	<	<
7	<	<	<	495	—	216	108
Non-opioid group							
8	20	30	43	18	30	39	—
9	<	20	20	20	20	<	27
10	25	<	18	<	40	20	<
11	23	50	30	22	20	16	27
12	<	<	<	<	—	<	28
13	<	<	<	<	<	<	<
14	27	<	<	20	<	<	<

1 = before anesthesia; 2 = after induction of anesthesia; 3 = 10 min after start of operation; 4 = 70 min after start of operation; 5 = 30 minutes after extubation; 6 = before start of PCA; and 7 = after PCA during a 4-h period. < = 15 or less.

Table 2. Substance P Levels in fmol·ml^{-1} during the Study Period

Pat. no.	1	2	3	4	5	6	7
Opioid group							
1	16.2	16.2	19.9	17.1	9.9	17.1	—
2	15.6	20.7	24.6	18.0	14.9	10.9	—
3	15.8	12.6	13.5	13.5	9.9	6.8	9.0
4	7.4	7.5	5.8	4.8	5.1	4.0–	5.6
5	5.8	5.5	6.1	5.2	5.4	4.0	—
6	6.4	9.5	11.0	7.2	—	8.5	6.3
7	7.0	8.3	4.8	8.6	—	9.6	11.5
Median	7.4	9.5	11.0	8.6	9.9	8.5	7.7
Non-opioid group							
8	15.3	11.7	11.3	11.7	12.6	14.9	—
9	13.8	14.3	2.9	10.8	10.8	10.8	13.5
10	12.3	9.5	5.4	3.9	7.2	5.4	6.3
11	10.8	10.4	17.1	7.6	11.9	15.3	16.1
12	6.0	8.1	7.3	9.9	—	6.3	6.0
13	10.8	9.0	6.6	7.4	63	59	20
14	8.6	9.9	9.5	9.7	9.5	10.6	9.0
Median	10.8	9.5	7.3	9.7	11.4	10.8	11.3

1 = before anesthesia; 2 = after induction of anesthesia; 3 = ten minutes after start of operation; 4 = 70 minutes after start of operation; 5 = 30 minutes after extubation; 6 = before start of PCA; and 7 = after PCA during a 4-hour period.

quirements. It might do so by changing the response to surgical stimuli and altering endogenous pain modulating mechanisms. Little information is available, however, regarding the fluctuations in CSF levels of neuropeptides over time. A study of the putative excitatory afferent transmitter (substance P) and a mu and delta receptor agonist [(Met)enkephalin-Arg^6-Phe^7] (13), therefore, could provide clues as to what changes take place during anesthesia and postoperatively during pain relief.

The changes in substance P and (Met)enkephalin-Arg^6-Phe^7 concentrations in CSF in the present study were small throughout the observation period, and did not reach statistical significance at any time. This is, of course, influenced by a type II error resulting from the small group sizes and the large interindividual variations.

The CSF samples were collected at a level in the subarachnoid space close to that of afferent input during surgery. Thus, they may be assumed to mirror the turnover of peptides at the spinal level. However, the time course of the turnover of peptides in the CSF compared with the changes at the nerve terminals is unknown. The absence of changes in CSF peptides in the present study is in accordance with a study by Waty et al. (14), in which anesthesia was found not to increase CSF immunoreactive beta-endorphin-like material or (Leu)enkephalin.

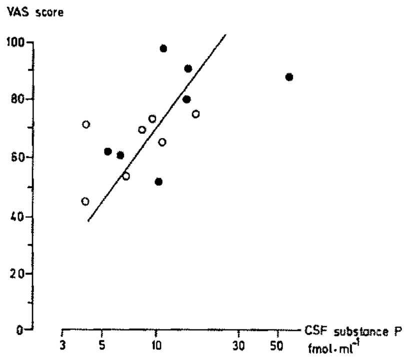

Figure 2. Correlation (r^2 = 0.383) between log concentrations of substance P in lumbar CSF and the pain assessments on the visual analogue scale (VAS) at the moment of maximal postoperative pain (before the start of PCA). Unfilled circles represent patients in the opioid group, filled circles represent patients in the non-opioid group.

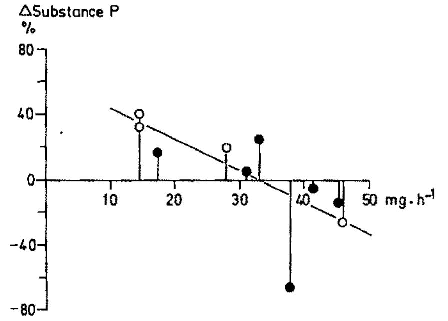

Figure 3. Inverse correlation (r^2 = 0.546) between the change in substance P concentration during the first 4 h of PCA and the consumption of opioid during PCA. Unfilled circles represent patients in the opioid group, filled circles represent patients in the non-opioid group.

Changes in CSF substance P and Fraction I endorphins have previously been shown to be small and inconclusive in the period between preoperative sampling and, 24 hours later, during the postoperative period (10). However, because CSF was sampled only twice (10), it could not be ruled out that the CSF concentrations may have varied during the 24 h with variable pain stimuli. As seen from the present study, the CSF concentrations of neuropeptides may vary considerably during surgery and in the presence of postoperative pain in some patients, but they remain relatively stable in most patients. One possible explanation for the absence of alterations in CSF concentrations is that changes in release of neuropeptides occur only very slowly. Another possibility is that the measured neuropeptides do not reflect activity in the dorsal spinal cord but may largely derive from supraspinal centers. Endorphin levels in CSF correlate with pain levels (14) and postoperative need for opioids (10). This could not be shown in the present study because of too little endorphin data.

The lumbar CSF concentrations of (Met)enkephalin-Arg^6-Phe^7 were below the limit of detection in about half of the patients during the whole period of observation.

CSF substance P concentrations usually varied little during the study period. There was no correlation between preoperative substance P levels in pain-free patients and demand for postoperative opioids. However, patients with high substance P concentrations at the time of their maximal postoperative pain (immediately before the start of PCA) rated their pain as more severe than patients with low substance P concentrations (Fig. 2). This supports the notion that substance P is involved in nociception. During PCA the patients in both groups who needed only small amounts of meperidine had increases in substance P CSF levels, whereas those who used large amounts of meperidine had decreases in CSF levels of substance P. It is consistent with the finding by Tamsen et al. (10) that the highest CSF levels of meperidine after PCA are seen in patients with the most pronounced decrease in CSF substance P. The decrease in substance P levels may be explained as a direct effect of the opioid on substance P release.

In summary, lumbar CSF concentrations of substance P and (Met)enkephalin-Arg^6-Phe^7) showed only small fluctuations during a 12-h period with highly variable pain stimuli. No significant difference in CSF concentrations was seen in patients given inhalation or neurolept anesthesia. In some patients, however, large intraindividual concentration variations were measured. Patients with high substance P concentrations at the time of maximal postoperative pain assessed their pain as being more severe than patients with low substance P concentrations before PCA. During PCA, those patients who needed only small amounts of analgesics had increases in CSF substance P levels, whereas those who needed large amounts of meperidine had decreases in CSF levels of substance P.

The absence of major changes in CSF neuropeptide concentration during surgery and postoperatively was unexpected. Apparently interindividual variations in neuropeptide output are considerable.

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1988;67:982–7

In Vitro Anesthetic Washin and Washout via Bubble Oxygenators:

Influence of Anesthetic Solubility and Rates of Carrier Gas Inflow and Pump Blood Flow

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NUSSMEIER NA, MOSKOWITZ GJ, WEISKOPF RB, COHEN NH, FISHER DM, EGER EI II. In vitro anesthetic washin and washout via bubble oxygenators: influence of anesthetic solubility and rates of carrier gas in flow and pump blood flow. Anesth Analg 1988;67:982–7.

The uptake and elimination of volatile anesthetic agents administered to patients under conditions of hemodilution and hypothermia during cardiopulmonary bypass have not been determined. To define the limitations imposed by oxygenators, we defined washin and washout curves for volatile anesthetic agents administered to bubble oxygenators primed with diluted blood (without connection to a patient). There was rapid equilibration of anesthetic partial pressure between delivered gas and blood (85–90% within 16 minutes). Increasing the gas inflow to the oxygenator from 3 to 12 L/min hastened washin and washout slightly, while increasing the pump blood flow from 3 to 5 L/min had no effect. Rates of washin and washout of anesthetics differed as a function of their blood/gas solubilities: enflurane>isoflurane>halothane during washin; isoflurane>enflurane>halothane during washout. However, these differences were small. Oxygenator exhaust partial pressures of anesthetic correlated with simultaneously obtained blood partial pressures, suggesting that monitoring exhaust gas may be useful clinically.

Key Words: ANESTHETICS, VOLATILE—isoflurane, enflurane, halothane.
SURGERY, CARDIOVASCULAR—cardiopulmonary bypass, oxygenators.

During cardiopulmonary bypass (CPB), volatile anesthetics are often added to the oxygen flowing through the oxygenator to provide anesthesia and to regulate systemic vascular resistance (1–4). Although oxygenators transfer oxygen and carbon dioxide well, their ability to transfer anesthetic gases has not been studied, i.e., the temporal course of anesthetic washin and washout in the blood delivered by oxygenators is unknown. Knowing the rate of washin would facilitate attaining a desired anesthetic concentration. The rate of washout is of concern because volatile anesthetics have depressant cardiovascular effects; therefore, it is usually desirable to reduce arterial partial pressure of the anesthetics before termination of CPB (2, 5). Knowing the time course of anesthetic washout would facilitate choosing the optimal time to discontinue anesthetic administration.

To define the anesthetic gas transfer characteristics of bubble oxygenators, we devised an in vitro model of hypothermic CPB and measured volatile anesthetic uptake and elimination in the hemodiluted perfusate of the CPB circuit. Five questions were addressed: (i) How rapid are washin and washout of isoflurane administered via a bubble oxygenator? (ii) Does rate of carrier gas inflow (oxygen) to the oxygenator affect washin and washout? (iii) Does rate of pump blood flow affect washin and washout? (iv) Does anesthetic solubility in blood affect washin and washout? And (v) does the partial pressure of anesthetic in oxygenator exhaust gas reflect the partial pressure in arterial blood?

Methods

Eleven cardiopulmonary bypass circuits were assembled, each consisting of a single roller pump, Ben-10®

This work was supported in part by a grant from Anaquest, a division of BOC, Inc.

Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication May 13, 1988.

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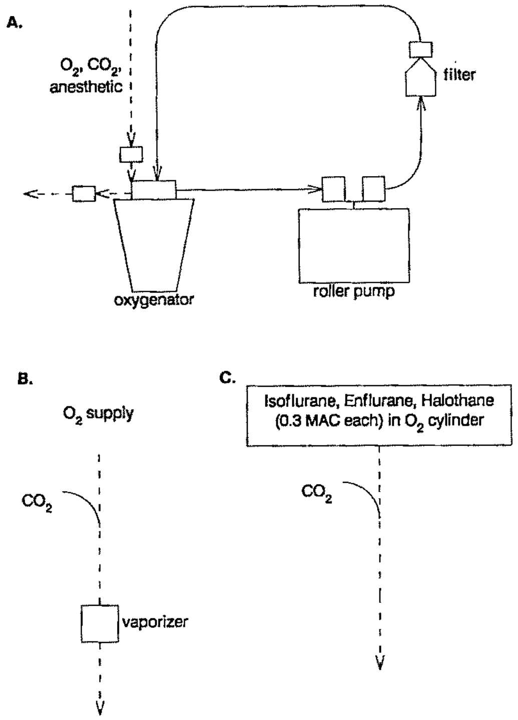
A.
O_2, CO_2, anesthetic
filter
oxygenator
roller pump
B.
O_2 supply
CO_2
vaporizer
C.
Isoflurane, Enflurane, Halothane (0.3 MAC each) in O_2 cylinder
CO_2

Figure 1. The simulated cardiopulmonary bypass circuit and the two methods of introducing volatile anesthetic to the oxygenator. (A) The schematic circuit: gas lines are dashed, perfusate lines are solid, and small rectangles represent sampling ports. (B) Isoflurane was introduced via a vaporizer placed in the gas inlet line. (C) Multiple anesthetics were added from a gas cylinder containing oxygen and 0.3 MAC each of isoflurane, enflurane, and halothane.

bubble oxygenator (Bentley Laboratories, Inc., Irvine, CA), arterial line filter, and the appropriate Tygon® tubing (Norton Co., Akron, OH) to connect these components (Fig. 1A). Circuits were primed with 700 to 900 ml of 5% dextrose in lactated Ringer's solution and human packed red blood cells, plasma, and platelets to yield a total circulating volume of ~2400 ml, having a hemoglobin concentration of 9.4 ± 0.6 g/dl. The gas flowing to the oxygenator was composed of a mixture of oxygen and sufficient CO_2 to maintain P_{CO_2} ≈40 mmHg (without temperature correction). Sodium bicarbonate, to adjust the pH to 7.35 to 7.45, and 5000 units of heparin were added. This blood perfusate was recirculated without attachment to a patient. Perfusate temperature was maintained at 24 to 26°C to simulate hypothermic CPB.

Volatile anesthetic agents were added to the gas inflow directed through the oxygenator in one of two ways (see Fig. 1B and 1C). When isoflurane was studied alone, a Fortec® (Cyprane, Keighley, UK) anesthetic vaporizer was inserted into the gas inflow line between the oxygen source and the oxygenator, according to usual clinical practice. During experiments examining uptake and elimination of concurrently administered anesthetic agents, oxygen and anesthetics (at 0.3 MAC each) were provided by a prepared compressed gas cylinder connected to the gas inflow line.

In all experiments, blood samples (5 ml) were withdrawn from the circuit via a stopcock located just distal to the arterial line filter. To measure anesthetic partial pressure in gas delivered to the oxygenator, gas samples were obtained through a stopcock in the gas inflow tubing just proximal to the gas inlet of the oxygenator. To measure anesthetic partial pressure in gas exiting the oxygenator, samples were withdrawn through a stopcock attached to the oxygenator's exhaust port. Samples of blood and gas were obtained just before the addition of anesthetic, and at 1, 4, 8, 16, and 32 minutes after beginning anesthetic administration (washin). Anesthetic was discontinued after 32 minutes and samples were obtained at the same intervals during washout. Blood-gas partition coefficients were determined in quadruplicate in each study (6).

Gas Flow Studies

Six oxygenators were used to examine the effect of gas inflow rate. The inflow was set at 3, 6, and 12 L/min, in random order, with pump blood flow held constant at 3 L/min. After each set of measurements, the gas inflow was changed.

Pump Flow Studies

Five additional oxygenators were used to examine the effect of altering the pump blood flow rate. The gas inflow rate was held constant at 3 L/min in these studies, while the pump flow rate was set at 3 or 5 L/min, the order randomly assigned. (Flows of 3 and 5 L/min were chosen to correspond to the range of pump flows normally used in adult patients, with 5 L/min approaching the mechanical limitations of the pump.)

Anesthetic Solubility Studies

To examine the effect of anesthetic solubility, a mixture of 0.3 MAC each of isoflurane, enflurane, and halothane in oxygen from a compressed gas cylinder was administered via the five oxygenators used for the pump flow studies. Only data obtained at constant and equal gas and pump flows (3 L/min) were analyzed.

Analysis of Samples

Anesthetic concentrations in all samples were determined by gas chromatography. Concentrations were

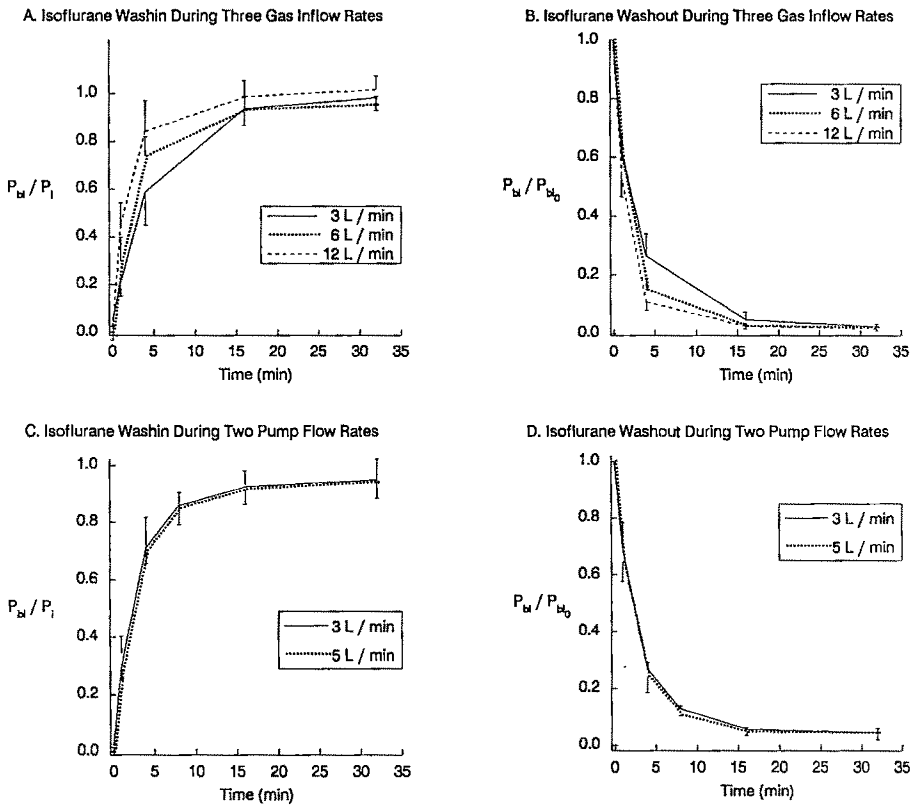

Figure 2. Washin and washout curves at various gas inflow rates (A and B), and pump flow rates (C and D). The partial pressure of isoflurane in blood (P_{bl}) is expressed as a ratio; the denominator is the simultaneously obtained inlet gas partial pressure (P_i) during washin (A and C), and the peak partial pressure in the sample obtained just before discontinuing anesthetic administration (P_{bl_0}) during washout (B and D).

converted to partial pressures, using the blood/gas partition coefficients determined in each experiment (6). Repeated-measures analysis of variance was used to determine whether anesthetic solubility or gas flow rate affected the speed of anesthetic washin and washout. We used the Neuman-Keuls test to determine differences among groups. Paired Student *t*-tests were used to determine whether pump flow rate had a significant effect. Differences were considered significant if $P < 0.05$. Linear regression analysis was used to examine the relationship between partial pressure of anesthetic in blood versus partial pressure in oxygenator exhaust gas.

Results

Blood/Gas Partition Coefficients

Mean blood/gas partition coefficients of isoflurane, enflurane, and halothane in hemodiluted human blood at 25°C were similar to those previously measured in undiluted human blood at normal body temperature (6–9) (Table 1).

Gas and Pump Flow Studies

Partial pressure of isoflurane in the blood perfusate equilibrated rapidly with that in the delivered gas (Fig. 2-A and 2-B). During washin, there was >50% equilibration by 4 minutes and >90% equilibration by 16 minutes at all gas inflow rates. Similarly, during washout, <25% of the peak concentration (the concentration at 32 min of washin) remained by 4 min and <10% by 16 minutes after discontinuing isoflurane administration. Washin of isoflurane was significantly faster at a gas inflow rate of 12 vs. 3 L/min during the initial 4 minutes of administration, but this difference was insignificant by 16 minutes.

Table 1. Solubility of Three Volatile Anesthetics in Human Blood

	Blood/Gas Partition Coefficients[a]		
	Hemodiluted at 25°C[b]	Undiluted at 37°C[c]	Undiluted at 22°C[c]
Isoflurane	1.16±0.15	1.46±0.09	2.85±0.24
Enflurane	1.75±0.21	2.11±0.14	4.43±0.37
Halothane	2.38±0.28	2.54±0.18	4.65±0.39

[a] Values are reported as mean ± SD.
[b] From present study.
[c] From Reference 4.

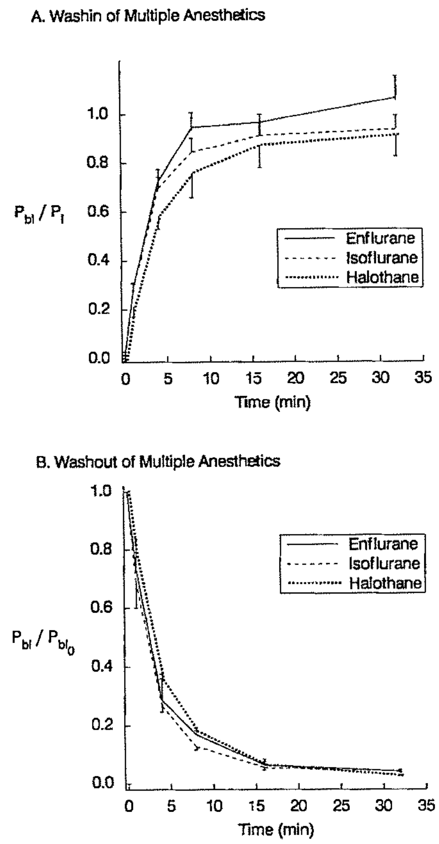

Figure 3. Washin and washout curves for three volatile anesthetic agents, isoflurane, enflurane, and halothane. The partial pressure of each anesthetic in blood (P_{bl}) is expressed as a ratio; the denominator is the simultaneously obtained inlet gas partial pressure (P_I) during washin (A), and the peak partial pressure in the sample obtained just before discontinuing anesthetic administration (P_{bl_0}) during washout (B).

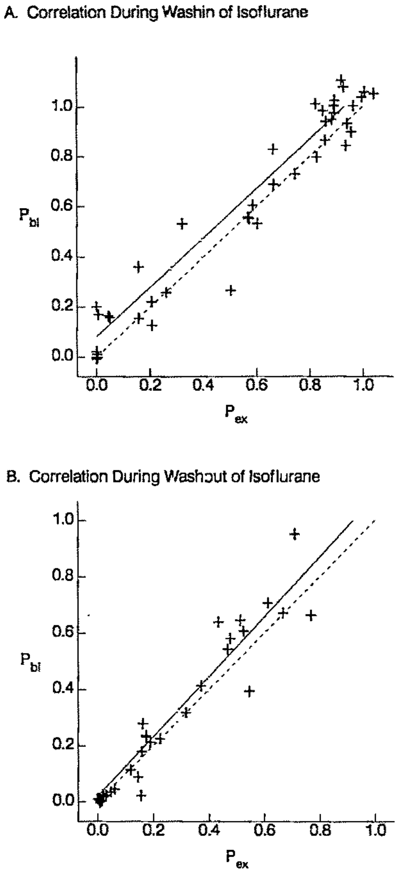

Figure 4. Correlation between the partial pressure of isoflurane in the blood perfusate (P_{bl}) v. the gas leaving the oxygenator (P_{ex}) during washin (A) and washout (B). The solid lines represent the relationship between blood and exhaust partial pressures of isoflurane, compared to the line of identity (dashed). For washin (A), the slope (± SD) of the regression line is 0.99 ± 0.04, and the standard error of the estimate is 0.09, $r^2 = 0.95$. For washout, the slope of the regression line is 1.06 ± 0.06, and the standard error of the estimate is 0.08, $r^2 = 0.92$.

Washout occurred significantly faster at gas inflow rates of 6 or 12 vs. 3 L/min during the first 16 minutes after discontinuing isoflurane administration; there was no difference by 32 minutes. Varying the pump flow rate did not significantly affect washin or washout of isoflurane (Fig. 2-C and 2-D).

Anesthetic Solubility Studies

Washin and washout of concurrently administered isoflurane, enflurane, and halothane were rapid (Fig. 3). For all anesthetics, the blood perfusate was >75% equilibrated with inlet anesthetic partial pressure by 8 minutes and 85–90% equilibrated by 16 minutes after beginning anesthetic administration. During washout, <20% of the peak concentration of any agent remained by 8 minutes and <10% remained by 16 minutes after discontinuing anesthetic administration. Washin of enflurane and isoflurane was significantly faster than that of halothane during the first 4 minutes; at 16 minutes, only enflurane was significantly faster. During washout, isoflurane was eliminated significantly faster than halothane during the first 8 minutes, but there was no difference by 16 minutes. The rate of washout of enflurane was intermediate to that of isoflurane and halothane, but not significantly different from either.

Relationship between Blood and Exhaust Gas Partial Pressures

Figure 4 illustrates the close association between the partial pressure of anesthetic in the blood perfusate and that in the oxygenator exhaust gas during both the washin and washout phases. During washin, the slope (±S.D.) of regression line equaled 0.99 ± 0.04, the standard error of the estimate (SEE) equaled 0.09, and $r^2 = 0.95$. During washout, the slope equaled 1.06 ± 0.06, SEE = 0.08, and $r^2 = 0.92$.

Discussion

Despite the frequent use of volatile anesthetic agents during CPB, factors that affect their uptake and elimination in this setting have not been previously defined. If increasing the rate of carrier gas inflow to the oxygenator is equivalent to increasing pulmonary ventilation, the result should be a more rapid washin and washout of anesthetic (10). In contrast, if increasing the pump flow is equivalent to increasing cardiac output, the result should be slower anesthetic washin and washout (11). In our in vitro model, increases in gas inflow did hasten washin and washout of isoflurane, as predicted; however, the increase was small. Increasing pump flow did not affect the rates of isoflurane washin or washout, perhaps because of nearly complete mixing in the oxygenator due to the relatively small blood volume and large pump flow of at least 3 L/min.

Differences among isoflurane, enflurane, and halothane in their rates of washin and washout would be expected, based on their differing blood/gas partition coefficients (7–9). Lower blood solubility results in a faster rise in arterial partial pressure of anesthetic with induction of anesthesia and a faster elimination during recovery. Therefore, anesthetic partial pressure in blood would be expected to equilibrate with its delivered gas partial pressure most rapidly with isoflurane, less rapidly with enflurane, and least rapidly with halothane. Several factors influence gas solubility in liquids. For example, gas is more soluble in blood at lower temperature (6, 12, 13); this might augment differences between these three agents in their rates of washin and washout during hypothermic CPB. Conversely, hemodilution, which occurs with onset of CPB when the crystalloid prime is added to the patient's blood volume, would exert an opposite effect on anesthetic solubility because anesthetics are less soluble in saline than blood (12–14). The blood/gas partition coefficients obtained in our in vitro model are similar to those previously measured in undiluted blood at normal body temperature (Table 1), probably due to counterbalancing effects of hemodilution and hypothermia. Washin and washout of isoflurane and enflurane were more rapid than those of halothane, as expected; the differences, although significant, were small. Washin of enflurane occurred more rapidly than that of isoflurane, despite the higher blood/gas partition coefficient of enflurane. The minor effects of varying gas flow, pump flow, and anesthetic agent are likely due to the absence of tissue uptake in this model, the relatively small volumes of blood and gas, and limited anesthetic uptake by the oxygenator (the difference between anesthetic partial pressure in blood exiting and reentering the oxygenator was probably very small).

The partial pressure of anesthetic in the exhaust gas correlated reasonably well with simultaneously obtained blood partial pressures of anesthetic. Analysis of anesthetic partial pressure in oxygenator exhaust gas (eg, with a mass spectrometer or infrared device) should reflect anesthetic partial pressure in blood during CPB. However, care must be taken in such sampling to assure accuracy and avoid risk to the patient. The improvised sampling port attached to the oxygenator's exhaust port must be airtight to prevent contamination of the sample from entrainment of room air and must allow for unimpeded gas egress, to avoid overpressurizing and bursting the oxygenator.

The total circulating volume in our in vitro model was much smaller (~2400 ml) than the total system volume of an adult patient undergoing CPB (~6500 ml), and there was no anesthetic uptake into patient tissues. Consequently, our in vitro model does not reflect the sum of what occurs in the clinical situation. However, the absence of the patient allowed us to define the limitation to transfer of anesthetics in bubble oxygenators. A time constant can be calculated for the oxygenator and compared to the washin and washout rates actually measured in our model. The time constant is the time required for the flow through a container to equal the capacity of the container (9); it is also the time required for a 63% washin or washout of a new gas and is given by:

$$\text{time constant of oxygenator} = \frac{\text{oxygenator capacity*}}{\text{gas inflow}}$$

For an oxygenator capacity of 6.4 L, and a gas inflow of 3 L/min, the time constant is 2.1 min. In fact, in our in vitro model, the time constant for all three anesthetics exceeded 3.1 min (Figs. 2 and 3), which suggests that the oxygenator is less efficient than would be predicted by its time constant. Therefore, washin and washout, although rapid, were slowed somewhat by a degree of oxygenator inefficiency, possibly caused by absorption of anesthetic into plastic components of the oxygenator, filter, and pump tubing (15). Limitation to anesthetic diffusion appears to be minimal, as indicated by the data presented in Figure 4.

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* We found the total volume of the oxygenator to be approximately 6 L. The gas volume of the oxygenator is the total volume minus the blood volume. The capacity of the oxygenator is the gas volume plus the product of the blood volume and the solubility of the anesthetic. Therefore, for isoflurane, if the total oxygenator volume is 6 L, the blood volume 2.4 L, isoflurane solubility 1.16, and the gas volume 3.6 L, the capacity of the oxygenator is 6.4 L.

During clinical CPB, the influences of tissue uptake of anesthetic during hypothermia and rewarming of the patient during the elimination phase also must be considered. Hypothermia not only increases the blood/gas solubility of volatile anesthetic agents in patients, but also increases tissue capacity for these agents. Both effects would be expected to slow the rate of rise of anesthetic partial pressure in arterial blood. Clinical studies will be required to evaluate the effects of such variables on anesthetic uptake and elimination.

The authors gratefully acknowledge the generous donation of Ben-10® oxygenators by Bentley Laboratories, Inc. (Irvine, CA), and the assistance of our perfusionists, William J. Nobles, Steven W. Hazel, and Kathleen M. Hamilton.

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Technical Communication

High Pressure and Anesthesia:

Pressure Stimulates or Inhibits Bacterial Bioluminescence Depending upon Temperature

Shuichi Nosaka, MD, Hiroshi Kamaya, MD, and Issaku Ueda, MD

NOSAKA S, KAMAYA H, UEDA I. High pressure and anesthesia: pressure stimulates or inhibits bacterial bioluminescence depending upon temperature. Anesth Analg 1988;67:988–92.

Although high pressure is often viewed as a nonspecific stimulus counteracting anesthesia, pressure can either excite or inhibit biological activity depending on the temperature at application. Temperature and pressure are two independent variables that determine equilibrium quantity, e.g., the state of organisms in terms of activity and anesthesia depth. We used the light intensity of luminous bacteria (Vibrio fischeri) as an activity parameter, and studied the effects of pressure and anesthetics on the bacteria's light intensity at various temperatures. The light intensity was greatest at about 30°C at ambient pressure. When the system was pressurized up to 204 atm, the temperature for maximum light intensity was shifted to higher temperatures. Above the optimal temperature for the maximal light intensity, high pressure increased the light intensity. Below the optimal temperature, pressure decreased light intensity. Pressure only shifts the reaction equilibrium to the lower volume state (Le Chatelier's principle). When the volume of the excited state is larger than the resting state, high pressure inhibits excitation, and vice versa.

Halothane 0.008 atm and isoflurane 0.021 atm inhibited the light intensity both above and below the optimal temperature. When pressurized, the light intensity increased in the high temperature range but decreased in the low temperature range, as in the control. Thus, high pressure seemingly potentiated the anesthetic action at low temperatures. When the ratio of the light intensity in bacteria exposed to anesthesia and those not exposed to anesthesia was plotted against the pressure, however, the value approached unity in proportion to the pressure increase. Because the light intensity under anesthesia approaches the control value at higher pressures regardless of the temperature range, pressure antagonizes anesthesia despite the apparent decrease in the intensity.

We conclude that (i) pressure is not simply an excitatory stimuli but can be inhibitory too, depending upon the temperature; also, that (ii) despite this dual effect, pressures up to 204 atm reverse anesthesia in this model over the temperature range 15 to 40°C.

Key Words: HYPERBARIA, ANESTHESIA REVERSAL. THEORIES OF ANESTHESIC ACTION—pressure reversal.

Pressure reversal of anesthesia was first reported by Eyring and Magee (1) and Johnson et al. (2) in 1942. Using luminous bacteria, both studies showed that pressure in the range of 100 to 150 atm reversed the anesthetic-induced suppression of bacterial light intensity. Although the effect of high pressure on anesthesia is well recognized, there is a tendency to treat high pressure as a simple stimulatory force. The high pressure nervous syndrome is generally considered to be caused by pressure's noxious stimulatory effect, and there have been efforts to relate high pressure effects with the actions of such pharmacologic excitatory agents as strychnine (3).

Pressure and temperature are two basic variables in

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Supported by the Medical Research Service of the Veterans Administration, and National Institutes of Health grants GM25716, GM26950, and GM27670.

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thermodynamics, and evaluation of the pressure effect without due consideration of temperature may lead to erroneous conclusions. In the present report, the light intensity of luminous bacteria was used to analyze the pressure effects in the presence and absence of two volatile anesthetics, halothane and isoflurane. Inhibition of the luminous bacteria by anesthetics has been well-documented (1,4–6). It will be shown that high pressure can either inhibit or excite, depending on temperature at the time pressure is applied.

Methods

Halothane was obtained from Ayerst (New York) and isoflurane from Anaquest (Madison, WI). Beef extract and peptone were obtained from Sigma Chemical Co. (St. Louis, MO) and agar from Fluka (Ronkonkoma, NY). All other reagents were the highest grade available.

Luminous bacteria, *Vibrio fischeri* (*Photobacterium fischeri*), obtained from Carolina Biological Supply (Gladstone, OR), were cultured on the peptone-agar medium using a modification of the method described by Nakamura et al. (7). The culture medium consisted of 15 g agar, 30 g NaCl, 0.2 g $MgSO_4{\cdot}7H_2O$, 2.5 g $CaCO_3$, 10 ml glycerol, 2 ml of 1 M phosphate buffer, pH 7, and added water to 1000 ml. The tube culture from the supplier was inoculated on the solid agar in a large (20 cm in diameter) culture dish and incubated for 16 hr at room temperature (24°C). After confirming a strong luminescence, the bacteria on the agar surface were harvested with a brush and suspended in a solution consisting of 3% (wt/vol) NaCl, 0.5% (vol/vol) glycerol, 0.25% $CaCO_3$ (wt/vol), and 62 mM phosphate buffer, pH 7. When kept on ice, the preparation was found to show constant luminosity for several hours after being warmed to the desired temperature.

The light intensity was measured by a photomultiplier assembly of a Hitachi Perkin-Elmer 139 spectrophotometer (Norwalk, CT) and a water-jacketed AMINCO high pressure cell with sapphire windows (Silver Spring, MD). The cell temperature was controlled by flowing water from a water bath through the cell jacket, and monitored by a Digitec thermometer with 0.01°C resolution (United Systems, Dayton, OH) in which the thermistor probe was inserted into a hole drilled into the body of the cell block.

The stock suspension was preincubated at the desired temperature for 15 minutes with bubbling oxygen with or without anesthetics, then transferred into the high pressure cell. Anesthetics were vaporized with oxygen in a copper kettle of an anesthesia machine. The anesthetic concentration, estimated from the kettle temperature and the flow of the carrier gas, was confirmed by a Shimadzu gas chromatograph (Columbia, MD) using a stainless steel column 1/8 in × 6 ft, packed with Porapak Q 80/100 mesh. A hand-operated hydraulic pump, filled with ligroin, was used to pressurize the system. The generated pressure was transmitted to the cuvette through a separator piston as previously described (8). The pressure was measured by an Autoclave Engineers digital pressure transducer system Model DPS-0201 (Erie, PA) with ±1 psi (0.07 bar) resolution. The experiments were done at four pressure levels: ambient, 68, 136, and 204 atm. (At this laboratory's altitude, ambient pressure is 0.84 atm.)

The bacterial light intensity is a function of the partial pressure of oxygen. Compression of the system by hydrostatic pressure, unlike compression by helium, increases oxygen partial pressure contained in the solution as microbubbles, and may change the light intensity. Nevertheless, because the present study is designed to compare temperature and anesthetic effects on the light intensity at the same pressure, possible changes in the oxygen partial pressure should not be a problem.

The light intensity was normalized by taking the value at 24°C as the control. All datum points were stored in an IBM PC microcomputer interfaced with PDP 11/23 minicomputer. The least squares linear regression analysis and the error estimates were performed with a statistics program.

Results

Figure 1 is the Arrhenius plot of light intensity of *V. fischeri* in the absence of anesthetics at four levels of pressure. The luminescence had an optimal temperature (30°C at ambient pressure) for maximal intensity. The optimal temperature shifted to a higher temperature with an increase in pressure. It is clear that the pressure increased the light intensity at higher temperature but decreased it at lower temperature.

To delineate the pressure-temperature relationships, Figure 2 is constructed by plotting the light intensity against the pressure at six temperature levels. The light intensity was normalized by taking the ambient pressure value at 24°C as 100. The light intensity was decreased by pressure when the temperature was 298 K (25°C) or lower, whereas it was increased when the temperature was 303 K (30°C) or higher.

Halothane and isoflurane inhibited the bacterial light intensity as earlier reported (5,9). The anesthet-

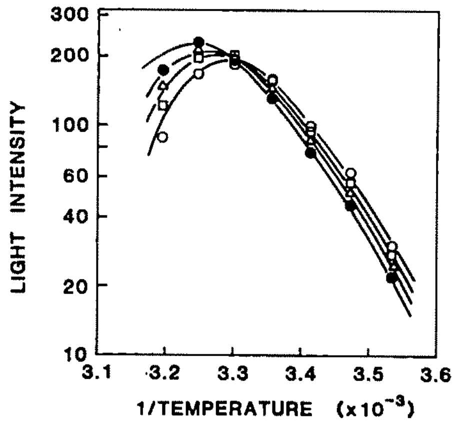

Figure 1. The effect of temperature on the light intensity of *V. fischeri* at four levels of pressure, plotted on the temperature coordinate (isobar activities). The light intensity was normalized by taking the maximum light intensity observed at ambient pressure as 100. The ordinate is the normalized light intensity plotted on a logarithmic scale and the abscissa is the reciprocal of the absolute temperature. Each point is an average of five independent experiments. The standard errors are within the size of the symbols. Hence, error bars are omitted. Pressures are ambient (0.84 atm) (○), 68 (□), 136 (△), and 204 atm (●).

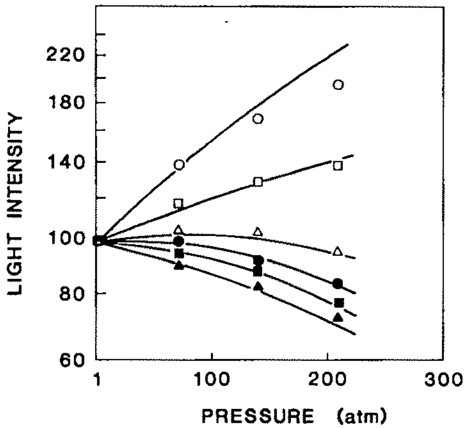

Figure 2. The effects of pressure on the light intensity of *V. fischeri* at six levels of temperature, plotted on the pressure coordinate (isothermal activities). The ordinate is the plot of the light intensity on the logarithmic scale. The intensity is normalized by taking the ambient pressure value as a standard. Each point is an average of five independent experiments. The standard errors are within the size of the symbols. Hence, error bars are omitted for the clarity of the figure. The abscissa is the pressure. The temperatures are 313 (○), 308 (□), 303 (△), 298 (●), 293 (■), and 288 K (▲). At higher temperatures, pressure increased the light intensity, but at lower temperature, pressure decreased the light intensity.

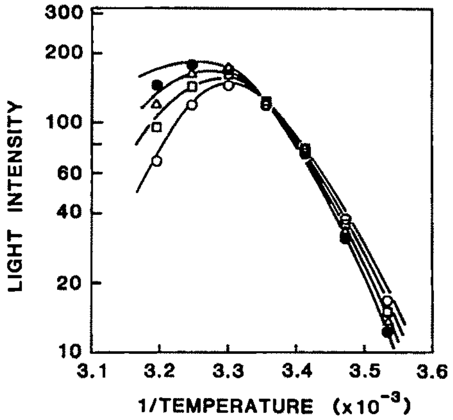

Figure 3. The isobar plot of the effect of temperature and pressure on the light intensity in the presence of halothane 0.008 atm on the light intensity of *V. fischeri*. The plot is similar to Figure 1. Pressures are ambient (0.84 atm) (○), 68 (□), 136 (△), and 204 atm (●).

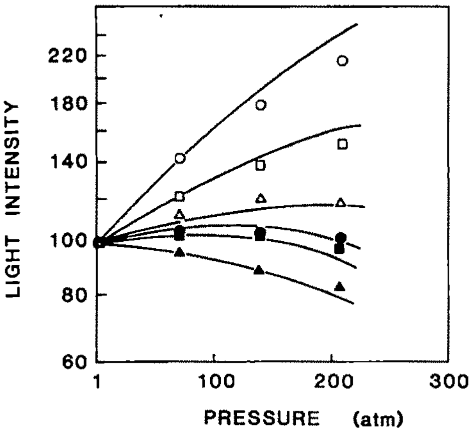

Figure 4. The isothermal plot of the effect of temperature and pressure on the light intensity in the presence of halothane 0.008 atm. The plot is similar to that of Figure 2. The temperatures are 313 (○), 308 (□), 303 (△), 298 (●), 293 (■), and 288 K (▲). Similar to the control, the pressure decreased the light intensity at lower temperature and increased it at higher temperature in the presence of halothane.

ic-pressure interaction was investigated at the anesthetic concentration that inhibited the light intensity by about 25%. At 24°C and ambient pressure, 25% inhibition was observed at the partial pressure of 0.008 atm for halothane and 0.021 atm for isoflurane.

Figure 3 is the Arrhenius plot of the light intensity in the presence of halothane at 0.008 atm partial pressure. As in the control study (Fig. 1), the plot produced maximum light intensity. The temperature for the maximum light intensity at ambient pressure was the same as the control, 30°C. The curves shifted to a higher temperature range with the increase in pressure. Figure 4 is the temperature-pressure relationship in the presence of halothane partial pressure 0.008 atm. The inhibitory action of pressure is evident below 293 K (20°C).

Discussion

The present results show that pressure is not a simple excitatory noxious stimulus that antagonizes anesthesia. Depending upon temperature, pressure becomes

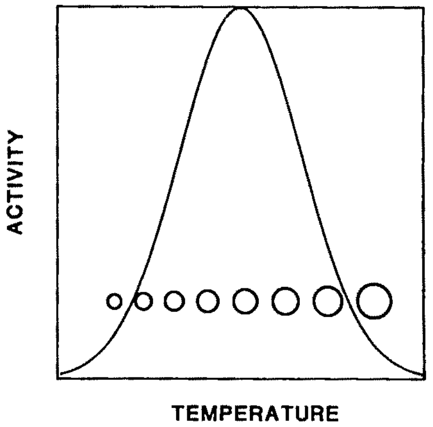

Figure 5. Schematic representation of pressure effect on biological activities. Ordinate is the biological activity in an arbitrary scale and abscissa is the temperature. Biological activity increases with the increase in temperature to reach a maximum value at an optimal temperature. Above this temperature, the activity starts to decline because of thermal inactivation. Meanwhile, the system volume (expressed by circles) increases steadily because of the thermal expansibility. Because the pressure pushes the equilibrium state to a smaller volume, the effect is excitatory at above the optimal temperature, but inhibitory below the optimal temperature.

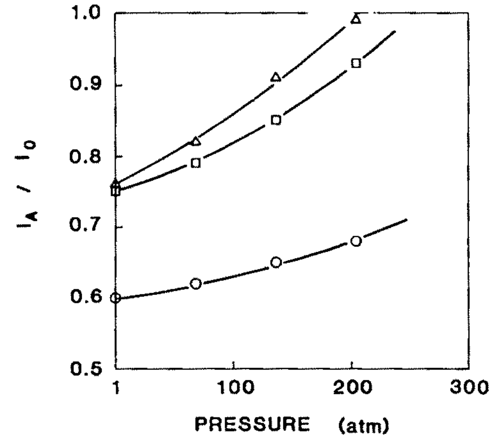

Figure 6. Analysis of the pressure effect on anesthesia. The ratio between the light intensity in the presence and absence of halothane 0.008 atm is plotted against the pressure at three temperatures; 30°C (△), 25°C (□), and 15°C (○). The ratio gradually approached unity by the pressure increase. This means that the anesthetic effect diminishes under high pressures in the low temperature range as well as in the high temperature range. Although the pressure appeared to enhance anesthetic inhibition at low temperatures, the pressure is antagonistic to anesthesia at any temperature. This figure also shows that anesthetic potency increases with the decrease in temperature.

inhibitory as shown in Figures 2 and 4. According to Le Chatelier's principle, pressure shifts the equilibrium state (such as the depth of anesthesia) to a smaller volume. Although the light intensity is a rate parameter and not an equilibrium quantity, the state of the enzyme associated with reduction in light intensity represents an equilibrium between the active and inactive portions. In this case, the equilibrium constant, K, has the following relationship with the pressure.

$$\left(\frac{\partial \ln K}{\partial P}\right)_T = -\Delta V/RT$$

Pressure exerts its effects upon biological activity only through reduction of system volume. The consequence is dictated by the activity of the smaller volume state. When the smaller volume state has higher activity, pressure's effect is excitatory. When the smaller volume state has lower activity, pressure is inhibitory. Figure 5 is a schematic representation of pressure's effect on biological activities, expressed as a function of temperature. With elevation of temperature, biological activity increases to reach a maximum at an optimal temperature. Above this temperature, the activity starts to decline as a result of thermal inactivation, while the system volume keeps increasing because of thermal expansibility. Because pressure only affects the total volume, activity decreases with pressure at temperatures below the optimal activity, but increases at levels of temperature above the optimal. In pressurizing animals, pain and fright would complicate this mechanistic picture, but should not vitiate the basic principle.

It is known that pressure can increase or decrease enzyme activity. With α-chymotrypsin, for example, pressure increased the equilibrium association constant between enzyme and the substrate, whereas pressure decreased the rate constant of the dissociation of the enzyme-substrate complex in the Michaelis-Menten reaction sequence (10). Because biological systems are composed of multiple enzyme reactions, pressure effects vary at each reaction step. Nevertheless, the overall effect is determined by the difference between the starting volume of multiple reactions and the final volume after the reactions.

The present low-temperature results appear to contradict the concept of pressure reversal of anesthesia. However, Figure 4 compares light intensity at ambient pressure with that at increased pressure. Because pressure alone decreases the light intensity at this temperature range, reduced light intensity under high pressure does not necessarily mean that the pressure augmented anesthetic potency. To evaluate the pressure-anesthetic interaction meaningfully, the light intensity during exposure to anesthetic must be compared with the control without anesthetic at an identical pressure.

Figure 6 shows the ratio of light intensity in bacteria exposed to anesthetics and in those not exposed plotted against the pressure. The ratio approached unity with increased pressure at both low and high temperatures. The light intensity in the presence of an anesthetic approached the control value when pressurized. This means that the anesthetic effect is always antagonized by pressure elevation. Thus, the present results support the concept of pressure reversal of anesthesia throughout the entire range of temperature, despite the illusive decrease in light intensity in bacteria exposed to an anesthetic in the presence of high pressure at low temperatures. Simon et al. (11) reported a similar observation with brine shrimp, *Artemia,* where both anesthetics and pressure reduced swimming activity. Because the anesthetic effect was less marked during periods of simultaneous exposure to both anesthetic and high pressure than it was during exposure to anesthetic alone, they concluded that pressure antagonism of anesthesia was demonstrable.

"Synergic or additive actions" between pressure and anesthetics have been reported (12). These reports, however, must be interpreted with caution because the observations were often made at a single temperature. It is possible that these studies were done at low temperatures, during which high pressure shows inhibitory effects. For this reason, pressure reversal of anesthesia requires definition. According to the current study, the pressure reversal of anesthesia is present when the plot between enzyme activity ratio [activity under anesthesia]/[activity of the control] and pressure shows a positive slope, i.e.,

$$\left(\frac{\partial(I_A/I_o)}{\partial P}\right)_T > 0$$

where I_A is the activity in the presence of anesthetics and I_o is the control activity without anesthetics.

Appendix

The activation enthalpy ($\Delta H^{\ddagger}$) and the thermal inactivation enthalpy change (ΔH) of the luminous enzyme can be estimated according to the theory of absolute reaction rate. The light intensity, I (13), is expressed as follows:

$$I = \frac{cT\exp(\Delta H^{\ddagger}/RT)}{1 + \exp(-\Delta H/RT)\exp(\Delta S/R)}$$

where c is a proportionality constant, T is the absolute temperature, R is the gas constant, and S is the entropy change.

The method of estimation each parameter is detailed in our publication on firefly bioluminescence (14). In brief, $\Delta H^{\ddagger}$ and ΔH are estimated from the slope of the Arrhenius plot of the light intensity at higher and lower temperature ranges, respectively. The rest of the values are determined by fitting $\Delta H^{\ddagger}$ and ΔH to the equation.

The obtained values at 0.84 atm were $\Delta H^{\ddagger} = 83.3$ kJ·mol^{-1}, $\Delta H = 210.1$ kJ·mol^{-1}, and $\Delta S = 691$ J·mol^{-1}·deg^{-1}. In the presence of halothane $8{\cdot}10^{-3}$ atm, the values were: $\Delta H^{\ddagger} = 87.5$ kJ·mol^{-1}, $\Delta H = 193.8$ kJ·mol^{-1}, and $\Delta S = 640$ J·mol^{-1}·deg^{-1}. The curves in Figures 1 and 3 were drawn using this equation and these values.

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ANESTH ANALG 1988;67:993–5

Clinical Reports

Use of Stellate Ganglion Blocks for Chronic Chest Pain Associated with Primary Pulmonary Hypertension

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Key Words: LUNGS—pulmonary hypertension. PAIN—chest pain with pulmonary hypertension. ANESTHETIC TECHNIQUES, REGIONAL—stellate block. SYMPATHETIC NERVOUS SYSTEM—stellate ganglion.

Stellate ganglion blocks have been successfully used for the treatment of a variety of sympathetically mediated acute and chronic pain syndromes (1). Longstanding primary pulmonary hypertension is usually associated with severe chest pain (2). Management of chronic chest pain in these patients has been unsatisfactory in most cases. We present a patient with primary pulmonary hypertension recently evaluated at our institution as a possible candidate for heart-lung transplantation who was initially considered to be unsuitable for transplantation because of likely poor postoperative compliance with medications due to dependence on narcotics used for management of her chronic chest pain. She was referred to our pain control center for management of her chronic chest pain and narcotic dependency before consideration for a possible heart-lung transplant candidate. We found that stellate ganglion blocks produced almost immediate and sustained pain relief and a clinically significant improvement in her pulmonary function studies.

Case Report

This 39-year-old woman was healthy until 7 years ago when she first noted mild fatigue that gradually progressed to exertional dyspnea and syncope. Four years before the current admission, cardiac catheterization established the diagnosis of primary pulmonary hypertension. When we saw her, her activities were very limited and she became dyspneic even at rest. She also complained of severe chest pain. She described the chest pain as sharp and constant in character and resembled "a distending balloon" in her chest cavity. In addition, she had anginal-type, substernal chest pain initiated by exertion. She also had diffuse sternal chest pain aggravated by gentle pressure on the sternum. The chest pain made the patient depressed and irritable. Using a visual analog scale, her subjective pain intensity rating was 40% at rest and 100% on exertion.

Past medical history included pylorospasm as an infant, hospitalization for meningitis as a teenager, and asymptomatic goiter as a young adult. Surgical history included a tubal ligation for multiparity. Her medications, all orally administered, included: furosemide, 40 mg daily, potassium supplement, 600 mg three times a day, methadone, 20 mg four times daily, oxazepam, 15 mg twice a day, and progesterone, 50 mg daily. She did not smoke or drink. She lived with her mother and three children. Her husband was paraplegic and lived in a home for the handicapped.

Her blood pressure was 130/90 mm Hg and her pulse rate was 98 beats/min. She was moderately obese. Palpation and percussion of precordial area elicited sharp pain. Her lungs were clear on auscultation. A right ventricular heave was present and there was a III/VI holosystolic murmur which changed slightly with respiration. She had a gallop rhythm. Neurological and musculoskeletal examinations were negative.

The patient was classified as Class III (high pathol-

Received from the Vanderbilt University Medical Center, Nashville, Tennessee. Accepted for publication April 28, 1988.

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ogy and high behavior profile) according to the Emory University Pain Classification (3) which categorizes pain not only from a pathological but also a behavioral standpoint.

The following treatment program was planned for management of this patient's chronic chest pain:

1. Psychological evaluation with counseling and reassurance
2. Right and left stellate ganglion blocks on different days
3. Pulmonary function studies before and after stellate ganglion blocks
4. Relaxation therapy
5. Inpatient narcotic detoxification protocol

Because time available for evaluation and treatment was limited (24 hours), a left stellate ganglion block (4) was performed using 10 ml 0.25% bupivacaine on the first day of evaluation with a right stellate ganglion block the next day. Pulmonary function studies were performed before and after each stellate ganglion block. On both occasions, she obtained immediate and sustained pain relief of her chest pain. In addition, there was improvement in her forced vital capacity though other pulmonary function tests remained essentially unchanged. Her general condition improved; her dyspnea and orthopnea decreased markedly and her ambulation improved significantly. She returned home later in the day in relatively stable and pain-free condition after her second stellate ganglion block.

She remained relatively pain-free for approximately 2 months. Her pain then recurred and an anesthesiologist in her home state repeated the stellate ganglion blocks with results comparable to those we had produced. She is currently taking no narcotics, is relatively pain-free, and is now on the waiting list for a suitable donor for heart-lung transplantation.

Discussion

Stellate ganglion blocks have been used in the management of chronic pain associated with Raynaud's disease and Raynaud's phenomenon (5), arterial insufficiency of the upper extremities (6), frostbite, acute vasospastic disorders (7), phantom limb pain of the upper extremity (8), herpes zoster and postherpetic neuralgia (9), some cases of trigeminal neuralgia (10), causalgia and reflex sympathetic dystrophy of the upper extremity (11), and some cases of atypical facial pain (12). The pharmacological sympathectomy produced by a stellate ganglion block may relieve pain by a variety of mechanisms (13). First, the increase in blood supply secondary to vasodilation in sympathetically denervated areas may relieve ischemic pain in cases of vascular insufficiency and frostbite. In cases of causalgia, reflex sympathetic dystrophy and pain mediated specifically via sympathetic efferents, pain relief may result from a decrease in the excitation of the sympathetic efferent fibers that in turn decrease the excitation of the internuncial pool of neurons in the lateral and anterior horns of the spinal cord (14), i.e., the pharmacological sympathectomy interrupts the "vicious cycle of reflexes" and consequently decreases the pain. In yet another group of patients, the results may involve both vascular and neurogenic effects.

The precise mechanism of action of pain control in our patient is not known. To the best of our knowledge, stellate ganglion blocks have never been used to treat the severe chest pain of primary pulmonary hypertension. It is possible that sympathetic fibers to the pulmonary vessels may be mediators of pain and that their consequent blockade may contribute to the patient's pain relief. Furthermore, the effect of stellate ganglion blocks on the pulmonary vasculature may decrease pain intensity in patients with chronic pulmonary hypertension. These were the tentative principles that formed the basis of treatment for our patient. Further studies are necessary to determine the mechanism by which stellate ganglion blocks relieve pain associated with chronic pulmonary hypertension.

In summary, we present the case of a patient with progressive primary pulmonary hypertension with severe chronic chest pain. She was treated with right and left stellate ganglion blocks and had immediate significant pain relief that lasted two months, at which time repeated stellate blocks were equally successful in relieving her chest pain. The mechanism by which stellate blocks relieve pain in this condition is unclear.

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Cardiovascular Effects of Lorazepam during Sufentanil Anesthesia

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Key Words: HYPNOTICS, BENZODIAZEPINES—lorazepam.

Sufentanil, an *N*4-substituted derivative of the synthetic narcotic fentanyl, provides hemodynamically stable anesthesia for cardiac surgery when used in high doses (1,2). Although high-dose opiate anesthesia is a well-accepted technique for cardiac surgery, incomplete amnesia and awareness are reported complications of this technique (3,4). Benzodiazepines, including diazepam and lorazepam, have excellent sedative and anxiolytic effects, and also provide amnesia (5,6). Because of this amnestic effect, a benzodiazepine is often added as an adjunct to narcotic anesthesia. The addition of diazepam to morphine or fentanyl anesthesia, however, may be associated with cardiovascular depression (7,8). Lorazepam, when used alone, is devoid of significant hemodynamic alterations (9,10). The cardiovascular effects of lorazepam in combination with the narcotic sufentanil have not been investigated. This study was undertaken to examine the cardiovascular effects of lorazepam when added to sufentanil anesthesia for coronary artery bypass graft surgery.

Methods

This study was approved by the Committee for Human Research at our institution and informed consent was obtained from all patients. Twelve patients who underwent coronary artery bypass grafting, ASA III and IV (age, 62 ± 7.6 years; weight, 80.9 ± 9.6 kg; mean ± SD), were studied. All were taking a calcium channel blocking drug before surgery and occasional nitroglycerin for angina. Two of the twelve patients were taking oral isosorbide and four of the twelve patients applied 2% nitroglycerin ointment on a regular basis before surgery. All patients were premedicated with morphine sulfate, 0.1 mg/kg intramuscularly, 1.5 hours before scheduled surgery. Patients received their usual dose of calcium channel blocking drug, isosorbide, and nitroglycerin ointment was applied at the time of premedication. On arrival in the operating room a vein was cannulated for administration of drugs and fluids, and a radial arterial catheter was placed. Heart rate and mean blood pressure were recorded and, together with the ECG, were continuously monitored. After preoxygenation by face mask, vecuronium, 0.01 mg/kg, was given intravenously. Sufentanil, 15 μg/kg, was then infused intravenously over 3–4 minutes. During injection of sufentanil an additional 0.15 mg/kg vecuronium was given intravenously. Each patient's trachea was intubated 5 minutes after beginning sufentanil infusion. After intubation a flow-directed pulmonary arterial catheter (Swan–Ganz) was placed via the right internal jugular vein by means of a Cordis introducer. Control measurements obtained 15 minutes after intubation included heart rate, mean arterial blood pressure, central venous pressure, cardiac output, pulmonary capillary wedge pressure, and systemic vascular resistance. The patients were then given lorazepam, 0.05 mg/kg intravenously, within a 30 second period. This dose is recommended in the lorazepam package insert when perioperative amnesia is desired. Cardiovascular measurements were repeated at 2, 5, and 10 minutes after infusion of lorazepam. Statistical analysis was made using analysis of variance for comparisons.

Results

The heart rate remained virtually unchanged from 69.9 ± 12.5 beats/min before induction to 68.3 ± 15.7 beats/min after intubation. The mean arterial blood pressure, however, decreased from 97.9 ± 16.7 mm Hg before induction to 84.3 ± 18.8 mm Hg after

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Received from the Department of Anesthesiology at the University of Kansas Medical Center, Kansas City, Kansas. Accepted for publication May 4, 1988.

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Table 1. Cardiovascular Dynamics During Sufentanil Anesthesia before and after Lorazepam*

	Control	2 minutes after lorazepam	5 minutes after lorazepam	10 minutes after lorazepam
Heart rate (beats/min)	62.9 ± 15.9	60.9 ± 15.1†	60.1 ± 15.3†	59.3 ± 15.0†
CO (L/min)	4.09 ± 1.12	4.02 ± 1.00	4.02 ± 1.13	4.05 ± 1.14
MAP (mm Hg)	83.1 ± 13.7	81.0 ± 14.0†	80.1 ± 14.4†	79.8 ± 13.6†
PCWP (mm Hg)	11.7 ± 2.9	11.5 ± 2.7	11.4 ± 2.6	11.7 ± 2.5
CVP (mm Hg)	8.2 ± 3.0	7.9 ± 3.2	7.8 ± 2.8	8.2 ± 2.5
SVR (dyn·sec·min^{-5}	1535.8 ± 412.4	1515.8 ± 422.1	1517.6 ± 448.6	1491.3 ± 426.7

[a] Abbreviations: CO, cardiac output; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; SVR, systemic vascular resistance.

*Lorazepam, 0.05 mg/Kg IV; all values are mean ± SD.

†$P < 0.01$.

induction and intubation, a statistically significant ($P < 0.001$) change.

The administration of lorazepam resulted in slight, but statistically significant decreases in heart rate and mean blood pressure (Table 1). Systemic vascular resistance also decreased slightly, but the change was not statistically significant. Cardiac output, pulmonary capillary wedge pressure, and central venous pressure remained virtually unchanged.

Discussion

The use of high doses of narcotics as complete anesthetic agents for cardiac surgery has become a common technique because of minimal effects on cardiovascular dynamics. Agents used and described for this technique include morphine (11), fentanyl (12,13), and, more recently, sufentanil (1,2). Incomplete amnesia and awareness are reported complications of this technique (3,4). Benzodiazepines, with excellent amnestic properties, are often added when high-dose narcotic techniques are employed. Previous studies, however, have reported that the addition of a benzodiazepine to a narcotic anesthetic resulted in cardiovascular depression. In one investigation the addition of two 5-mg intravenous doses of diazepam in patients who had received 1.5–2.3 mg/kg morphine intravenously for open-heart or major vascular operations resulted in significant decreases in arterial blood pressure and heart rate and an increase in systemic vascular resistance (7). Another investigation demonstrated that 10-mg diazepam administered intravenously as an adjunct to high dose fentanyl anesthesia (50 μg/kg) resulted in significant decreases in stroke volume, cardiac output, arterial blood pressure, and systemic vascular resistance in patients undergoing mitral valve replacement (8). Patients undergoing coronary artery bypass surgery given 0.125, 0.25, or 0.5 mg/kg of diazepam intravenously followed by an infusion of fentanyl, 50 μg/kg, developed significant decreases in mean arterial pressure and systemic vascular resistance during fentanyl infusion whereas control patients given only fentanyl did not demonstrate these hemodynamic changes (14). All of these investigations described a significant decrease in mean arterial blood pressure, but only one study reported a decrease in the cardiac output (8). Thus, the decrease in mean arterial pressure cannot be attributed to a direct myocardial depressant effect of diazepam in the other two studies (7,14) because cardiac output remained virtually unchanged. The decrease in mean arterial pressure may be caused by diazepam's ability to decrease circulatory plasma levels of both epinephrine and norepinephrine (14). The differing results of these studies may be attributable to the use of different narcotics, the administration of the drugs in different orders, or different doses and/or techniques of administration of diazepam.

In each of these studies the benzodiazepine used as an adjunct to the narcotic anesthetic was diazepam. Studies reporting the hemodynamic effects of diazepam alone differ greatly in their results. Mean arterial pressure has been reported to decrease (15–17) or remain unchanged (18–20) after intravenous administration of diazepam. Cardiac index has been reported to remain unchanged (15,17,18) or decrease (16,17). Heart rate has been reported to decrease (21), increase (16), or remain unchanged (15,18). The basis for the varying results is not known, but it may be due to differences in the dose of diazepam given and/or rates of its administration.

Lorazepam was chosen in this study as the benzodiazepine to supplement sufentanil because of the hemodynamic stability with which it is associated when used alone (9,10), and because the amnesia effect lasts longer than with diazepam (20,22). The amnesia effect of diazepam typically lasts about 2 hours; for lorazepam it lasts 4 hours and longer.

In our study of lorazepam administered to patients anesthetized with large doses of sufentanil, there were statistically significant but only slight decreases in heart rate and mean arterial blood pressure when lorazepam was given. There were no other significant cardiovascular changes. With this specific benzodiazepine–narcotic combination, the addition of the amnestic agent was not at the expense of cardiovascular stability. This, as mentioned above, is in contrast to previous studies that combined the benzodiazepine, diazepam, with high-dose morphine or fentanyl.

A previous report, in contrast to our study, described four cases of sudden hypotension on induction with sufentanil in patients about to undergo cardiac surgery (23). All patients had received lorazepam, 2.5 mg intravenously before induction with sufentanil. It was hypothesized that the lorazepam given before and in combination with the sufentanil was a major cause of the hypotension reported in these cases. The present study did not support this hypothesis. The reason for the hypotension in these four cases is not known, but it may have been because lorazepam was administered before the sufentanil infusion. In our study, lorazepam was given after sufentanil anesthesia was established and hemodynamics were stable.

We conclude that lorazepam may be used as an adjunct to sufentanil anesthesia without adverse hemodynamic changes. Sufentanil–lorazepam appears to be an attractive narcotic–benzodiazepine combination as a high-dose narcotic anesthetic technique because of its ability to provide relatively stable hemodynamics and still allow the inclusion of the amnestic effect of a benzodiazepine.

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Hypoventilation Caused by Ventilator Valve Rupture

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Key Words: EQUIPMENT, VENTILATORS

We describe the malfunction of an anesthesia ventilator with resulting significant hypoventilation and hypercarbia. The patient system relief valve of the standing bellows ventilator on a Dräger Narcomed 2A® anesthesia machine was the cause of the malfunction.

Case Report

Following an uneventful induction of anesthesia and tracheal intubation in a 20-year-old, 60-kg man scheduled for aortic valve replacement, ventilation was controlled with a Dräger AV-E®, standing bellows ventilator. The fresh gas flow was oxygen 6 L/min, and the ventilator was set to deliver tidal volume 750 ml at rate 10/min, with inspiratory to expiratory ratio 1:2. The minimum ventilatory pressure alarm was set at 8 cm H_2O. Peak airway pressure was 10 cm H_2O, and arterial blood analysis revealed pH of 7.32, PCO_2 57 mmHg, and PO_2 460 mmHg. Neither the volumeter reading of the exhaled tidal volume nor filling of the bellows during exhalation were noted. The oxygen gas flow was reduced to 3 L/min, tidal volume was increased to 850 ml/breath, and ventilatory rate was increased to 12/min. Within a minute the minimum ventilatory pressure alarm sounded. Peak airway pressure was 7 cm H_2O, exhaled tidal volume was 200 ml/breath, and the ventilator bellows did not fill completely during exhalation. Arterial blood gases revealed pH 7.30, PCO_2 60 mmHg, and PO_2 481 mmHg. The patient was ventilated manually without difficulty, and no leak in the breathing circuit was detected. When mechanical ventilation was reinstituted, however, the bellows did not rise completely during exhalation. The anesthesia ventilator was checked for leaks. The hose from the ventilator to the scavenger system was disconnected. It was noted that gas was flowing from this hose during inhalation and exhalation. Subsequently the patient system relief valve was inspected and was found to be ruptured, causing it to become incompetent (Figs. 1 and 2). The patient was ventilated manually, the valve was replaced, and mechanical ventilation was reinstituted. Normal mechanical ventilation was confirmed by a tidal volume 900 ml/breath, peak airway pressure of 18 cm H_2O, a full ventilator bellows at end exhalation, and normal arterial PCO_2. The remainder of the operation proceeded uneventfully and the patient suffered no adverse effects from the period of hypoventilation.

Discussion

Numerous case reports have described hypoventilation that resulted from ventilator malfunction, human error, or both (1–3). Causes of ventilator-associated hypoventilation include leaks (4,5), failure to cycle (6), occlusion of the hose from the common gas outlet of the anesthesia machine (7), and scavenging system malfunction (8–10). To our knowledge, this is the first report of hypoventilation induced by a ruptured patient system relief valve (PSRV).

The PSRV of the Dräger AV-E® ventilator closes during inspiration and opens during exhalation after the bellows has filled (Fig. 3). During inspiration, the PSRV closes and prevents gas escape from the breathing circuit to the scavenger. As the bellows compresses, gas flows toward the patient and the lungs expand. During exhalation, the valve remains closed until the bellows fills with exhaled and fresh gases. Once the bellows has filled during exhalation, the PSRV opens and excess gas is released from the ventilator.. The source of the excess gas is fresh gas from the anesthesia machine delivered in excess of patient uptake.

In this case, the PSRV was ruptured, causing loss of gas from the ventilator during both inspiration and

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Received from the Department of Anesthesiology, New York University Medical Center, New York, New York. Accepted for publication May 16, 1988.

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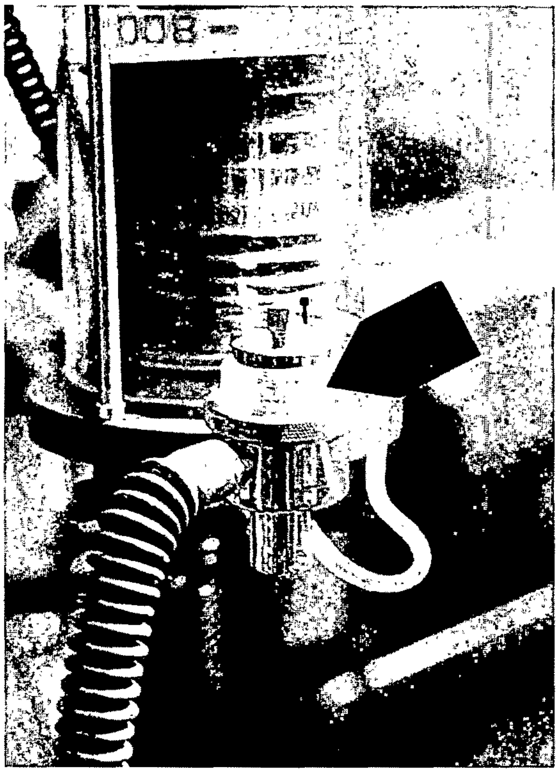

Figure 1. View of Dräger standing bellows ventilator from the rear. The arrowhead indicates the patient system relief valve (PSRV).

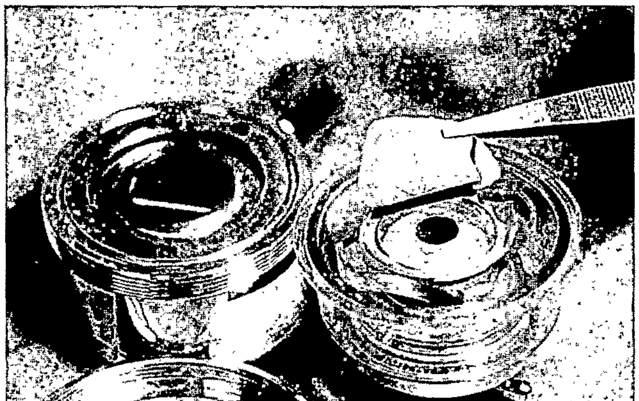

Figure 2. Ruptured patient system relief valve. Forceps indicate area of rupture.

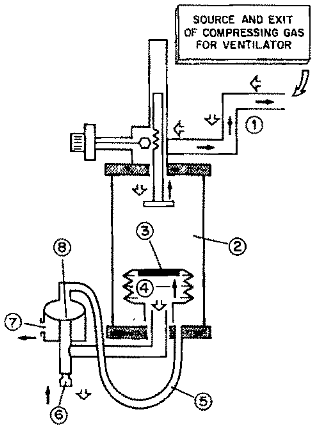

Figure 3. Schematic diagram of Dräger AV-E standing bellows ventilator. 1 = Pipeline for ventilator compressing gases. 2 = Bellows chamber of ventilator. 3 = Top of the bellows. 4 = Bellows. 5 = Plastic tubing connecting bellows chamber to PSRV. 6 = Connection to breathing system. 7 = Connection to scavenging system. 8 = Patient system relief valve. Open arrows indicate flow of gas during inspiration. Closed arrows indicate flow of gas during expiration.

exhalation. The ventilatory effect was a reduction of tidal volume, peak airway pressure, and minute ventilation, with resultant hypercarbia. In addition, the ventilator bellows did not fully expand because of the valve's rupture and the consequent loss of ventilating gases. The cause of the valve rupture is not known, but it may have been due to wear and tear from extensive use, or fatigue of the rubber caused by exposure to the potent anesthetic vapors, nitrous oxide, and oxygen. Cleaning solutions and improper handling of the valve may also have caused it to fail.

Although the ruptured PSRV caused ventilator malfunction, the anesthesiologists could have prevented hypoventilation. A thorough preoperative check of the anesthesia equipment would have revealed the ventilator malfunction and provided an opportunity for the valve to be fixed, or the machine replaced, prior to anesthesia induction.* When testing the ventilator one should place a reservoir bag on the patient end of the breathing circuit. The bag should intermittently fill and empty as the ventilator cycles and the bellows rise completely during exhalation. Failure of the bellows to rise indicates a leak in the system. Intraoperatively, one should have detected the ventilator leak by noting the partially filled bellows, and the patient should have been manually ventilated until the problem was corrected. Before placing a patient on a ventilator, the anesthesiologist should always check the inspiratory pressure his "educated hand" requires, while observing chest movement. Peak pressure on the ventilator should correlate with the original observations. If the peak pressure is substantially different, it may be due to ventilator malfunction.

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* Food and Drug Administration: Anesthesia Checkout Recommendation. August, 1986.

The problem was localized to the ventilator because no leak in the breathing system occurred when the patient was manually ventilated. The PSRV malfunction was suspected when gas was heard and felt moving down the scavenger hose during both inspiration and exhalation. As noted previously, gas should exit the breathing system only during exhalation and after the bellows is completely full. It is worth noting that the operating manual for this ventilator contains no recommendation with regard to routine maintenance of this valve.

In summary, a case of hypoventilation due to ruptured PSRV is presented. Preoperative ventilator check would have revealed the defect and the machine could have been changed. If not recognized before induction of anesthesia, rupture of the PSRV will be recognized by noting gas flow from the ventilator to the scavenger during inhalation. If failure of the PSRV is detected intraoperatively, patients should be manually ventilated until the valve is replaced.

The authors wish to thank Drs. Sanford Miller and Jan Purgess for their assistance in reviewing and editing the manuscript.

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1988;67:1002–4

Multiple Nerve Palsies after Anesthesia and Surgery

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Key Words: COMPLICATIONS—diabetes, nerve palsies.

Peripheral nerve injuries during anesthesia are usually preventable. Although complete recovery from such injuries can be expected, it is important to guard against their occurrence (1). Injuries of the brachial plexus or its peripheral branches are the most common of all perioperative neurologic complications (1). They can occur at various levels of the plexus or in the periphery. The peripheral nerves most frequently injured in the perioperative period are the radial and ulnar nerves (2–5).

Perioperative nerve injuries are usually caused by stretch or extrinsic compression of a nerve (6,7). Other possible mechanisms of injury include ischemia and transection. Isolated radial nerve injuries can also be caused locally by edema in the intraneuronal compartment (intraneuronal closed-compartment syndrome) in the absence of extrinsic compression or stretch (8,9).

We present a case in which bilateral wrist drop developed after an emergency surgical procedure performed under general anesthesia. To our knowledge, no case of this kind has been reported previously. In this patient, dysfunction caused by preexisting disease might well have been confused with a complication possibly related to intra-operative positioning anesthetic management.

Case Report

A 30-year-old, 96-kg diabetic man was admitted for placement of an insulin pump and possible pancreatic transplantation. The patient had juvenile-onset diabetes mellitus and had required insulin since the age of seven. Diabetic complications included: diabetic retinopathy and retinal detachment, the latter corrected with laser surgery; renal failure with successful kidney transplantation 6 months before admission; and peripheral neuropathy including paresthesia involving the distal parts of all four extremities. Two days before the operation neurologic examination revealed slight decrease of pinprick sensation in the left hand, bilaterally normal proprioception, and good motor strength bilaterally. Electromyography (EMG) 6 months earlier revealed bilateral carpal tunnel syndrome with involvement of median nerves bilaterally. In addition, EMG showed evidence of generalized peripheral neuropathy. The EMG was not repeated preoperatively because the patient did not complain of an increase in subjective symptoms.

The patient had a subcutaneous insulin infusion pump and required 108 U/day of regular insulin. He was treated with prednisone, 20 mg/day, cyclosporine, 1150 mg/day, and theophylline, 300 mg three times per day. He was a nonsmoker with no history of cardiac, liver, or neurologic disease other than the peripheral neuropathy of the upper extremities. He was allergic to penicillin.

Physical examination revealed that the patient had a functional arteriovenous (AV) fistula in the left arm. The chest and heart were normal, and no wheezing was heard. Results of laboratory tests included hemoglobin, 14.4 g/dl, hematocrit, 42.2%, potassium, 4.0 mEq/L, and blood glucose, 410 mg/dl. Chest roentgenogram and electrocardiogram were normal. He was scheduled for orthotopic pancreas transplantation. The patient ate 7.5 hours before surgery and received prednisone (20 mg), cyclosporine (1150 mg), and trimethoprim-sulfamethoxazole (100 mg).

On arrival at the operating room the patient was anxious, with a blood pressure of 220/110 mm Hg (during this hospital admission his blood pressure had been 140–150/80–90 mm Hg), pulse was 90 beats/min, and respiratory rate 14 beats/min. A 16-gauge

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Received from the Department of Anesthesiology/Critical Care Medicine, University of Pittsburgh School of Medicine, University Health Center of Pittsburgh, Pittsburgh, Pennsylvania; and the Loyola University Medical Center, Chicago, Illinois. Accepted for publication May 2, 1988.

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intravenous catheter was inserted on the dorsum of the right hand.

Preinduction monitoring included an automatic blood pressure cuff on the right arm, cycling every 5 minutes; five-lead ECG; and precordial stethoscope. A large pad was carefully placed on the left arm to protect the AV fistula, and good bruit was heard after placement and positioning. Both elbows were padded with eggcrate foam; both arms were internally rotated and placed at the patient's side. After 3-mg *d*-tubocurarine, anesthesia was induced with thiopental (375 mg), followed by succinylcholine (120 mg), for tracheal intubation. Anesthesia was maintained with O_2, N_2O, and isoflurane. A total of 20 mg pancuronium, 42 mg curare, and 800 mg fentanyl was given during the 9.5-hour procedure.

After induction, additional monitoring devices were placed, including esophageal and rectal temperature probes, a peripheral nerve stimulator on the left side of the face, a ventilator disconnect alarm, an O_2 alarm, and a mass spectrometer. For heat preservation, a blood warmer, a warming blanket, and a humidifier were used. A 20-gauge right radial arterial catheter was inserted. The arms were repositioned at the patient's side within 15 minutes of induction, and automatic blood pressure cuff recordings correlated well with measurements made via the arterial catheter. The blood pressure cuff was then deflated.

The operation began 20 minutes after induction, and a 16-gauge central venous catheter was placed in the right internal jugular vein with the patient in the Trendelenburg position. Blood pressure was 140/80 mm Hg after induction of anesthesia, and the patient remained hemodynamically stable throughout the procedure, which lasted 9.5 hours. Blood loss was 1100 ml; intravenous fluids included 700 ml dextrose (5%) in lactated Ringer's solution, 2100 ml 0.9 normal saline, and 1000 ml dextrose (5%) in 0.5 normal saline. Urine output was 825 ml. Intraoperatively, blood glucose was maintained between 250 and 350 mg/dl using a continuous intravenous insulin infusion at 6–7 U of regular insulin per hour. Upon anastomosis of the grafted pancreas, the insulin infusion was stopped, and the glucose level remained at about 200 mg/dl. The patient's temperature remained between 36° and 37°C. At the end of the procedure, neuromuscular blocking agents were reversed with 0.4 mg glycopyrrolate and 10 mg pyridostigmine, and the patient was taken to the postanesthesia recovery room (PAR). The trachea was extubated without complication shortly thereafter.

In the PAR, the patient was unable to grasp the bed siderails or to extend either wrist. A neurologist found that the patient had severe bilateral radial nerve palsies, moderate bilateral ulnar paresis, and mild bilateral median nerve paresis. The patient also had distal hypalgesia, hypesthesia, and loss of proprioceptive sensation in the fingers. Motor and sensory deficits were more severe on the right side than on the left. The proximal muscles of both arms had normal motor function. The neurologist recommended placement of bilateral cock-up splints and physiotherapy, both of which were instituted. After 6 months the patient improved partially with physiotherapy and splinting. After 2 years, the patient still had right-wrist drop with radial and median nerve involvement, left-wrist drop, less severe than on the right, and slight motor involvement of the ulnar nerve. Electromyography at this time revealed generalized peripheral neuropathy, multiple entrapment neuropathies of median and peroneal nerves bilaterally, and neurogenic changes most compatible with right radial neuropathy and involvement of all three nerves on the left.

Discussion

Postoperative peripheral neuropathies are generally related to the anatomic positioning of the patient in the operating room and pressure applied to the nerve in the perioperative period (1). Such neuropathies can occur also during movement of the patient from operating table to bed. Predisposing factors include diabetes, alcoholism, periarteritis nodosa, herpes zoster, hypotension, hypothermia, application of a tourniquet, duration of surgery more than 6 hours, use of neuromuscular blocking agents, and a postulated hereditary factor (1,2,5,7,10,11).

Muscle relaxants decrease or eliminate normal skeletal muscle tone, and thus the arms may be kept in a position for a longer time than the stretched nerves can tolerate (11–13). Hypothermia decreases the blood flow of the vasa nervosum (5,14). In most cases, the postoperative onset of neurologic symptoms occurs within the first 24 hours (1). Trauma to the nerves can occur after placement of venous or arterial catheters (9). The median nerve can be injured by an intravenous catheter or blood pressure cuff or by pressure applied by constricting adhesive tape (1). Recovery time is about 6 months in more than 90% of patients who have splinting and physiotherapy.

Obviously, the best measure for postoperative peripheral neuropathy is prevention (6,13). Abduction of the arm should be limited to less than 90°. However, brachial plexus injury has been reported with the arm abducted as little as 60°. External rotation compresses the brachial plexus in the space between the first rib and clavicle (13). All pressure points on the arm and leg should be padded. The surface of arm boards should be at the same level as the operating table, and arm boards should not be used in the Trendelenburg position because they may increase the leverage over the brachial plexus (1,6,13), pushing the head of the humerus against the brachial plexus (15). The brachial plexus is best protected by positioning the arms at the sides with draw sheets or padded arm guards. The use of shoulder braces can increase the risk of brachial plexus injury, even when the arms are at the side (13,16,17).

In our patient, the postoperative bilateral nerve lesions were diffuse and patchy, and not at one specific site, implying no pressure point injury. Bilateral wrist drop argues against blood pressure cuff compression as a cause, because the cuff was placed only on the right arm; it was used for only 15 minutes and then deflated. Because the arterial catheter and the cuff were on the same side, cuff inflation would have interfered with the tracing of the arterial pressure wave form. All precautions were taken to prevent injuries caused by positioning under anesthesia. Despite these measures, bilateral radial nerve palsy occurred in this patient.

A well-known complication of diabetes mellitus, mononeuritis multiplex involves single large nerve trunks, distal to their plexus of origin, causing cutaneous hypoesthesia or hyperesthesia as well as paralysis (18). Mononeuritis may occur even in mild cases of diabetes. It is caused by infarction within the nerves. These nerve infarctions are almost always asymmetric, though multiple nerves may be affected. Pain is common at the onset of vascular neuropathies, usually with an acute onset and variable periods of progression and exacerbation. Recovery usually occurs, but slowly, over many months.

Another possible cause of the bilateral wrist drop that occurred postoperatively in our patient is accumulation of interstitial fluid compressing the vasa nervosum, already compromised by long-standing diabetes. The long duration of the operation (9.5 hours), during which the patient was paralyzed (preventing muscular movement and promotion of circulation) may also have contributed to the occurrence of wrist drop.

In summary, a case of multiple nerve palsies after anesthesia and a prolonged surgical procedure in a diabetic man is presented. The patient had preexisting neuropathies, and despite the ample care taken to prevent nerve injury, bilateral multiple nerve palsies occurred, which partially resolved over time. The suspected causes of these findings include mononeuritis multiplex and interstitial fluid accumulation due to prolonged surgical time and immobility.

The authors thank Lisa Cohn for editorial assistance.

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ANESTH ANALG 1005
1988;67:1005–7

Factitious Malignant Hyperthermia

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Key Words: HYPERTHERMIA—malignant.

Malignant hyperthermia (MH) is an inherited disorder. Evidence of susceptibility includes a history of an MH episode or a positive halothane/caffeine contracture test in a first-degree relative. An MH crisis may be precipitated by halogenated anesthetic agents and/or depolarizing muscle relaxants. In addition, stress is a known initiator of MH crises in certain individuals. The classical diagnostic triad consists of skeletal muscle rigidity, metabolic acidosis, and elevated body temperature.

The following is a case with historical evidence of MH susceptibility and multiple clinical episodes resembling MH that responded to appropriate medical management. However, this patient proved to have factitious MH.

Case Report

A 19-year-old woman, otherwise in good health, presented to another hospital with a right upper quadrant puncture wound allegedly received while swimming in the ocean. Initial exploration under general anesthesia revealed multiple glass fragments and a 4-cm carpenter's nail. She underwent several more abdominal wall explorations without incident. However, the abdominal wound persisted in spite of seemingly appropriate medical and surgical management. After approximately 4 weeks of treatment she was transferred to our medical center with a diagnosis of pyoderma gangrenosum, and where she was initially treated with 40 mg/day of oral prednisone.

The remainder of her history, physical examination, and laboratory data were unremarkable except for a family history of MH susceptibility. She reported her identical twin sister and one other of her six siblings had positive halothane/caffeine skeletal muscle contracture tests performed at a reputable testing center.

Three days after admission she required an emergency exploratory laparotomy for an intraabdominal abscess. Because of her family history, it was decided to use non-triggering anesthetic agents and to pretreat her with dantrolene, 1 mg/kg IV. Although the surgical procedure was uneventful, dantrolene was continued for 24 hours postoperatively (4 $mg \cdot kg^{-1} \cdot day^{-1}$ in divided doses).

Further abdominal debridement was scheduled 8 days later. She was anesthetized with a 2-chloroprocaine (3%) epidural and given dantrolene prophylaxis as before. Two hours postoperatively she developed musculoskeletal rigidity, tachypnea, and a sinus tachycardia of 180 beats/min. In addition her temperature increased from 36.7°C to 37.7°C in 15 minutes. A diagnosis of stress-induced MH was made. She was given IV diazepam, an endotracheal tube was placed and dantrolene, 4 mg/kg IV, was administered. Nasogastric ice lavage was begun. Arterial blood gas analysis revealed hypocapnia and a metabolic acidosis (base excess, −14 mEq/L; the other blood gas values were lost from the medical record), which was treated with sodium bicarbonate IV. Controlled ventilation was used and a respiratory acidosis never developed. Her maximum temperature was 38.2°C. She was admitted to the intensive care unit for monitoring and observation. Blood samples were obtained for measurement of serum CPK levels.

The following evening she again became rigid after repeated emesis. During this event her heart rate increased from 140 to 180 beats/min. Therapy included mask ventilation with 100% O_2, dantrolene (4 mg/kg IV), sodium bicarbonate (50 mEq IV), and nasogastric ice lavage. The rigidity subsided after 20 minutes. Arterial blood gas analysis after 40 mEq sodium bicarbonate revealed a metabolic alkalosis (pH 7.48, Po_2 262 mm Hg, Pco_2 37 mm Hg). Her maximum temperature was 37.2°C. Serum CPK val-

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The opinions expressed herein are the opinions of the authors and should not be construed as the opinion of the Department of the Army or the Department of Defense.

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ues in blood samples drawn in the previous 48 hours were all within normal limits. She was kept in the intensive care unit for another 48 hours for observation.

Over the next two weeks, she underwent two additional debridements using 2-chloroprocaine (3%) epidural anesthesia. After the second procedure she developed an episode of musculoskeletal rigidity that was observed by a group of physicians. It appeared to all present that the episode terminated because of patient fatigue. Several moments later she again developed rigidity, which was treated with verbal reassurance and minimal sedation (diphenhydramine [Benadryl] 50 mg IV). Dantrolene was withheld. Arterial blood gas tensions and CPK values from these episodes were within normal laboratory limits.

Over the next 2 weeks she exhibited six more "episodes" of rigidity that responded to verbal reassurance and diphenhydramine sedation. Cultures from her abdominal wound consistently grew multiple fecal organisms. Follow-up with her family revealed the patient had no twin sister and no family history of MH susceptibility. She was transferred to the psychiatry service for further evaluation. Diagnoses of chronic factitious disorder and borderline personality with suspected self-multilation were made.

Discussion

To our knowledge, there are no other reported cases of a factitious disorder presenting as episodes of malignant hyperthermia. The patient had access to information concerning MH because of recent training as a practical nurse. We assume this was where she acquired sufficient knowledge to be able to deceive her physicians successfully. Because of the increasing awareness of the disorder in the public sector, it is possible that other cases may occur.

Stress-induced MH in the postoperative period after a trigger-free anesthetic has been reported (1). The clinical signs our patient developed during her first "episode" were fairly convincing. A metabolic acidosis is considered to be the hallmark of an MH episode (2). This, in addition to her family history, made a diagnosis of stress-induced MH likely. In retrospect, the most likely explanation for the acidosis, tachycardia, and increase in temperature was increased metabolic demand from her voluntary efforts to maintain whole-body rigidity for a prolonged period of time. The absence of hypercarbia during these events could have been detected with end-tidal CO_2 analysis (3); it was not available at the time this case occurred. The normal CPK values raised questions about the diagnosis of MH, although episodes of MH without evidence of rigidity and rhabdomyolysis are well documented (4). Concern that the diagnosis was incorrect prompted telephone calls to the MH testing center and to the family, and the history was confirmed to be false. In spite of these revelations and two events that resolved without dantrolene treatment, there remained considerable controversy as to whether to withhold dantrolene during future "episodes."

It is now apparent that in caring for the MH-susceptible patient, it might be advisable for the anesthesiologist to contact the testing center that is supposed to have established the MH diagnosis. First, the testing center can validate the historical data. Second, the clinician should find out which test was used to make the diagnosis. There are several diagnostic tests for MH; currently, the only test validated by independent laboratories is the halothane/caffeine contracture test (5–10). Third, the testing center may provide guidance on the advisability of proceeding with planned surgery and on specific aspects of management.

Malignant hyperthermia is a potentially fatal disorder that, if recognized early and treated appropriately, today carries a mortality rate of only 7% (11). On the other hand, diagnosis is often difficult, and empiric treatment with dantrolene is expensive and potentially dangerous (2). Unfortunately, this case expands the differential diagnosis for perioperative hyperthermia. However, with the knowledge of this presentation, aggressive historical follow-up and the use of continuous end-tidal CO_2 monitoring, the factitious presentation of MH should easily be established.

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1988;67:1008–10

Use of Repeated Nerve Blocks in Management of an Infant with Kawasaki's Disease

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Key Words: COMPLICATIONS, KAWASAKI'S DISEASE. ANESTHESIA, PEDIATRIC—regional. ANESTHETIC TECHNIQUES, regional, sympathetic block.

Kawasaki's disease, sometimes called mucocutaneous lymph node syndrome, is an acute febrile illness of childhood most common in the first year of life. It was first described by Kawasaki in 1967 (1) and has since been reported in the American and Japanese literature (2). The syndrome generally presents with a prominent necrotizing vasculitis component with aneurysms of the coronary arteries and proximal medium-size peripheral arteries (3). We report here the potential usefulness of repeated peripheral and central conduction blocks to provide regional sympathectomy in management of the peripheral vascular complications in an infant with Kawasaki's disease.

Case Report

The patient was a seven-month-old who developed a viral syndrome and otitis media. These were treated with amoxicillin and later with a combination of trimethoprim and sulfamethoxazole (Bactrim) about one month before admission. At about this time his mother noted that he had stopped weight bearing. Two weeks before admission, he developed bilateral conjunctivitis, which was treated with topical sulfisoxazole. Eleven days before admission he began coughing and vomiting. A chest x-ray at that time was interpreted as consistent with *Chlamydia* pneumonia and treatment with a combination of erythromycin ethylsuccinate and sulfisoxazole (Pedazole) was begun. One day before admission, he again developed bilateral otitis media; vomiting continued. His mother noted cyanosis of all toes and an intermittent temperature of 38.5°C.

At the time of admission the child was somewhat irritable, but in no acute distress. Weight was 7.6 kg, temperature 38°C, pulse rate 150 and regular, respiratory rate 36/min and blood pressure 92/40 torr. Pulses were full in all proximal vessels. The chest was clear and the heart showed a grade III/VI systolic murmur from the left lower sternal border to the apex. All nail beds were deeply cyanosed, as were the first, second, and fourth toes bilaterally. Chest x-ray showed an enlarged heart and echocardiogram showed massively dilated coronary arteries. A diagnosis of Kawasaki's disease was made.

Therapy with gamma globulin and a low dosage of aspirin was started. Four days later the patient developed ischemic EKG changes with loss of R waves in V5 and V6. He also developed a new S3 gallop. A day later, peripheral cyanosis progressed to involve the right forearm and hand and both legs and feet. A high dosage of methylprednisolone was started (20 $mg \cdot kg^{-1}$/day) as was nifedipine and low dose heparin. Although there was initial improvement, his condition gradually worsened over the next 5 days. Fluorescein studies showed no distal flow in the right forearm and hand or in either foot or lower leg.

On day 11 we were asked to see the patient to determine if peripheral blood flow might be improved by sympathetic blocks. After ascertaining by examination that there were no axillary arterial aneurysms and that the partial thromboplastin time (PTT) was within normal limits, we performed a right axillary brachial plexus block using a 25-g needle and 5 ml of 0.25% bupivacaine, and a caudal block, using 5 ml 0.25% bupivacaine at 8:30 p.m. There was an immediate improvement in the color of the right hand and forearm and of both lower legs and the left foot. These improvements persisted for approximately 12 hours, but the distal blood flow, as judged by color, appeared to worsen again and both procedures were repeated on day 12 at 10:30 a.m., provid-

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Received from the Acute Pain Management Service, Pain Control Center, University of Massachusetts Medical Center, Worcester, Massachusetts. Accepted for publication May 17, 1988

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ing marked improvement in color of the hand and both lower extremities noted again. Left brachial plexus block was delayed because of concern about systemic local anesthetic toxicity. Two hours later, a left axillary brachial plexus block was also performed that resulted in an improvement of the color of the left hand. The caudal and the right axillary blocks were repeated four hours later. Each time the blocks were performed a change in sensitivity to pain as assessed by withdrawal from skin pinch indicated correct placement of the block. The general level of agitation in the patient was diminished after each block and was thought to be associated with a reduction in the amount of pain the patient was experiencing in the ischemic extremities.

At 11:00 p.m., lower limb blood flow studies were carried out using fluorescein dye before and after the caudal block. These were as follows (in ml/min):

	Before		After	
	Left	Right	Left	Right
Thigh	71	54	72	70
Leg	48	8	56	9
Foot	25	0.7	36	0.7

Since there appeared to be no further improvement in the distal blood flow on the left, and because the color of the right foot now remained better, we elected to perform no further caudal blocks. Because the appearance of both hands improved and remained improved after the series of brachial plexus blocks, no additional blocks were performed. The patient was fully heparinized at this point.

Angiography performed on day 15 indicated severe narrowing of the right common iliac artery, a left iliac artery aneurysm, and complete occlusion of the distal right common-femoral artery. Ultimately the patient underwent amputation of the right forefoot and the left middle finger. He is now doing well.

Discussion

The etiology of Kawasaki's disease is not known, but several viral and, recently, bacterial agents have been implicated (4). The pathology of the peripheral vascular changes involves inflammatory changes in the extraparenchymal portion of elastic arteries that produce periarterial inflammation and medial destruction with narrowing of the vessel lumen (5). Five of the six principal diagnostic criteria must be present to establish the diagnosis of Kawasaki's disease: (i) fever persisting five days; (ii) injection of the conjunctiva; (iii) inflammation of the oropharynx; (iv) peripheral extremity changes, which may include induration, reddening, or edema, as well as desquamation of peripheral extremities; (v) truncal rashes; and (vi) cervical lymphadenopathy. Development of a new cardiac murmur suggestive of mitral insufficiency, EKG changes, and peripheral vascular insufficiency are often ominous signs.

Management of this disease has been primarily supportive, involving high-dose aspirin (up to 100 $mg \cdot kg^{-1}/day$) both to control fevers and, in the subacute phase, to inhibit platelet aggregation. Low dose aspirin (5 to 10 $mg \cdot kg^{-1}/day$) is thought to suffice for the latter. Prevention of thrombosis within the aneurysms will, it is believed, prevent vascular occlusion and the resultant ischemia distal to the occlusion in the coronary arteries as well as in the arteries of the extremities. Treatment with a high dosage of corticosteroids is controversial because of a reported increased mortality in patients treated with steroids and a possible association of steroids with the formation of coronary artery aneurysms (4). It is not clear, however, whether risk actually increases simply because patients so treated were already at higher risk because of more serious disease.

In our case, the management of the peripheral ischemia by use of caudal blocks to provide pharmacologic or chemical lower extremity sympathectomy and brachial plexus blocks for upper extremity sympathectomy represents a different approach to the management of vascular complications. In two previous reports, recommendations had been made for the use of stellate ganglion (6) and caudal blocks (5), but in the former case consent was refused and in the latter case there was no improvement with the caudal. It may have been that the caudal block was performed too late in the course of the disease and that the vasculitis and arterial occlusion had progressed too far. In our case, however, the blocks clearly made an important difference in the upper extremities and may have made an improvement in the left foot. It is not clear whether demarcation of the right foot was at a lower level because of the use of the caudal blocks, but the clinical impression was that the ultimate amputation was more distal as a result of improved blood flow after placing the blocks.

It seems important to consider several factors before deciding to use nerve block techniques in the management of this disease. If the patient has myocardial ischemia, the same attention to hemodynamic stability must be given as it is given to the adult patient with occlusive coronary artery disease undergoing any anesthetic procedure. Proper attention must be given to the coagulation profile in any patient who has been treated with heparin or inhibitors of platelet function. If a perivascular technique such as axillary or subclavian perivascular brachial plexus block is planned, the arterial landmarks must be examined for evidence of aneurysmal dilatation. We elected to use axillary brachial plexus block for the upper extremities because of the relative ease of performance of this block in children and because no anatomical abnormalities could be detected. Stellate ganglion block could have been performed, but little information exists as to the requisite volumes for this block in children and it would not have provided any sensory endpoint for the detection of the correct performance of the block in the event that there was no improvement in the blood flow to the extremity.

Considerable attention must be paid to the toxicity of the drugs administered in the performance of multiple blocks. Each time we performed a combined caudal and brachial plexus block in our patient we injected a total of 25 mg bupivacaine or 3.2 mg/kg. This is certainly a maximum allowable dose, but the volume of local anesthetic in individual blocks would have been barely adequate to provide surgical anesthesia (7).

We feel that the provision of extensive and prolonged sympathectomy of the extremities in our patient resulted in an improved outcome in that the loss of one finger and the distal one third of one foot represented far less than would have been lost had peripheral blood flows not been kept up with the block procedures. One previously reported attempt to manage the peripheral complications of Kawasaki's disease with peripheral sympathectomy did not meet with success, whereas ours did. This can most likely be attributed to earlier use of the technique in our case. It is also clear that infants can indeed be responsive to chemical sympathectomy, which should perhaps be considered more widely in the management of peripheral vascular insufficiency in infants in other states such as vascular spasm following trauma. We believe that peripheral or central conduction block may be helpful in reducing the ischemic tissue loss associated with Kawasaki's disease.

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ANESTH ANALG 1988;67:1011–14

Monitoring of Intraoperative Cerebral Hemodynamics before and after Arteriovenous Malformation Resection

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Key Words: ANESTHESIA, NEUROSURGICAL—cerebral A-V malformations. BRAIN, BLOOD FLOW—cerebral A-V malformations.

Hyperemia and subsequent hemorrhage in relatively normal brain is a major source of postoperative morbidity and mortality following resection of arteriovenous malformations (AVM) (1,2). After resection, blood flow diverted from the AVM vascular bed may be routed into tissue unable to autoregulate blood flow effectively, which could result in hyperemia or intracerebral hemorrhage. The clinical syndrome of hyperperfusion has been termed perfusion pressure breakthrough (3). Techniques available to monitor for hyperperfusion would be of value in perioperative management of these often complicated cases. It was hypothesized that patients who develop postoperative perfusion pressure breakthrough would show evidence of increased cerebral blood flow (CBF) intraoperatively after obliteration of the arteriovenous shunt.

Methods

This investigation was approved by the Institutional Review Board of Columbia Presbyterian Medical Center. Informed consent was obtained from 11 patients scheduled to undergo elective AVM resection. Anesthesia was induced with thiopental (4 mg/kg) and tracheal intubation facilitated with vecuronium or pancuronium. Anesthesia was maintained using 0.75–1.25% isoflurane in 6:4 nitrous oxide/oxygen. Monitoring included a capnograph, ECG, temperature probe, blood pressure transduction, and arterial blood gas determination. Blood pressure was maintained at approximately 10–20% below preoperative values and an effort was made to maintain isoflurane concentration at 0.75%. All CBF measurements were made with the isoflurane inspired concentration stable for at least 1 hr (except for one measurement as noted in Table 1).

The CBF device was the Novo Cerebrograph 10a® (Novo Diagnostic Systems, Bagsvaerd, Denmark) (4). For the purposes of this study, only two detectors were used. One detector was fixed ipsilateral to the AVM, 5 to 6 cm remote from the operative site but within the same major arterial distribution territory. The other detector was fixed contralaterally in an equivalent homologous position. In one patient (case 1), it was not possible to use the contralateral detector for technical reasons.

Approximately 20 mCi of ^{133}Xe in sterile saline was injected intravenously for each CBF measurement. This dosage resulted in peak count rates between 1000 and 3000 counts/5-sec interval. A catheter was advanced into the endotracheal tube for sampling of end-tidal gas and the resultant air radioactivity curve was used in deconvolution of the head curves and to correct for recirculation of tracer. Clearance was recorded for 11 minutes. Correction for remaining activity with multiple CBF determinations was performed (4). Data were transferred to a PDP 11/73 computer so that individual head curves and corresponding curve fitting could be visually inspected. CBF data were analyzed and expressed as the Initial Slope Index (ISI). The ISI (5,6) is derived from a monoexponential fit performed on a theoretical curve

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Presented in part at the Annual Meeting of the International Anesthesia Research Society Annual Meeting, San Diego, CA, 1988. Supported in part from a Research Starter Grant from the American Society of Anesthesiologists and a Biomedical Research Support Grant, Columbia University and National Institutes of Health, SO7-RR-D5395-25.

Received from the Departments of Anesthesiology, Psychiatry, Neurology, and Neurological Surgery, Columbia University College of Physicians and Surgeons, New York, New York. Accepted for publication June 6, 1988.

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Table 1. Physiological Data for Ipsilateral and Contralateral CBF (IPSI, CONTRA CBF, ml·100g^{-1}·min^{-1}), inspired isoflurane concentration (ISO %), hemoglobin (HGB, g/dl), temperature (°C), Pa_{CO_2} (mmHg), and mean arterial pressure (MAP, mmHg)

	IPSI CBF		CONTRA CBF		ISO%		HGB		TEMP		Pa_{CO_2}		MAP	
Patient	A	B	A	B	A	B	A	B	A	B	A	B	A	B
1[a]	26	50	●	●	0.75	0.75	14.9	14.9	35.8	36.7	28.0	27.0	90	76
2	25	39	22	24	0.75	0.75	15.3	14.3	35.1	35.5	32.2	30.3	66	76
3	20	27	22	33	0.75	0.75	14.3	12.0	35.5	36.9	21.5	27.0	64	62
4[b]	22	69	21	68	0.75	1.25	12.3	11.7	35.3	35.9	27.0	34.6	69	70
5	24	38	23	39	0.75	0.40[c]	11.7	11.0	34.5	34.6	25.0	23.0	63	72
6	28	37	34	41	1.25	1.25	11.7	9.7	35.3	37.0	25.3	25.0	77	61
7	25	23	21	26	1.00	1.00	9.7	9.7	36.4	36.9	21.0	21.1	81	80
8	21	37	21	40	0.75	1.00	9.5	9.5	34.4	35.6	23.4	24.1	87	74
9	18	19	17	19	0.75	0.75	14.7	13.8	35.2	36.7	23.4	22.8	77	71
10	22	32	20	31	0.75	0.75	11.3	11.0	35.7	36.4	23.7	23.3	79	81
11	22	26	18	23	0.75	0.75	9.7	10.1	35.0	35.9	21.6	23.2	68	69
Mean	23.0	36.1[d]	21.9	34.4[d]			12.3	11.6	35.3	36.2[d]	24.7	25.6	75	72
SD	2.9	14.0	4.6	14.1			2.2	2.0	0.6	0.8	3.3	3.4	9	7

A = PRE, B = POST; ● = not available.

[a] Patient developed postoperative brain swelling.

[b] Patient developed postoperative intracerebral hemorrhage.

[c] In this case, isoflurane administration was discontinued 10 minutes prior to CBF measurement and the concentration is only approximate.

[d] Significantly greater than PRE (A) value.

constructed for a biexponential solution (7,8) for the experimental data and expressed in ml·100g^{-1}·min^{-1}, for a blood brain partition coefficient of unity (6).

After exposure of the dura, an initial CBF measurement (PRE) was made. After resection of the AVM was completed, CBF was again measured (POST). Values for PRE and POST were compared using paired Student's *t*-tests. This was done for both the entire group of patients and with the two cases with complications excluded. A *P* value of <0.05 was taken as significant. All values are expressed as mean ± SD.

Results

Three men and eight women, ages 34 ± 9 years and weight 67 ± 13 kg, underwent surgery for moderate to large cortical AVMs. Average size of the lesions was roughly 3.5 × 3.0 × 2.5 cm. The locations of the AVMs were temporal (five patients) parietal (four patients), frontal (one patient), and occipital (one patient). Physiologic data and CBF results are shown in Table 1 and Figure 1. The PRE, CBF, and other physiological data were similar for all patients. All procedures were uneventful intraoperatively, and no patient emerged from anesthesia with new neurological deficits. There were two adverse late postoperative outcomes clinically attributable to perfusion pressure breakthrough. Patient 1, who underwent a right temporal-occipital AVM resection, developed confusion and lethargy over the course of several days and had significant brain swelling and midline shift in the ipsilateral frontal region on CT scan, corresponding to the area under the intraoperative CBF detector. He fully recovered by the eighth postoperative day. There was no evidence of residual AVM on postoperative angiography. Patient 4 underwent removal of a large temporal AVM. She did well until 6 hours postoperatively, when she experienced an intracerebral hemorrhage (ICH) and was immediately reexplored. However, 6 hours later she suffered a second ICH and never regained brain stem function. No residual AVM was found at postmortem. Of importance is the fact that neither of these patients developed overt postoperative arterial hypertension.

In the nine patients without postoperative complications, ipsilateral CBF significantly increased from 22.8 ± 3 to 31 ± 7 ml·100 g^{-1}·min^{-1} from PRE to POST. Contralateral CBF also increased similarly. Blood pressure, Pa_{CO_2}, and Hgb did not differ, but temperature increased significantly by a mean of 0.9°C. The two patients with complications had large (92 and 213 percent) increases in ipsilateral CBF after AVM resection. Similar increases in contralateral CBF were observed.

Discussion

The risk of morbidity from untreated cerebral AVM approaches 50% (1). Advances in surgical and anes-

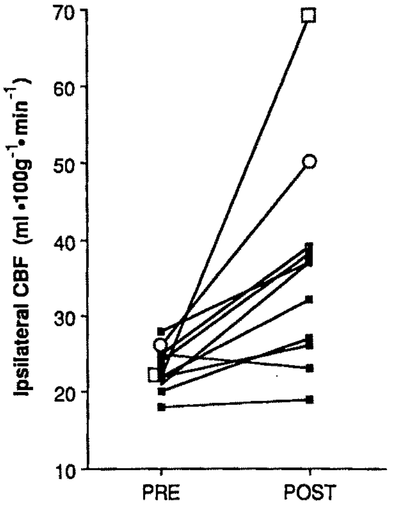

Figure 1. Individual changes in CBF from the before AVM resection (PRE) to after resection (POST). Cases with clinical evidence of perfusion pressure breakthrough, patient 1 and 4, are shown by a square and circle, respectively.

thetic management have greatly reduced this figure, even with lesions in relatively deep brain structures (9). Monitoring techniques that serve to further increase the safety of operative intervention are valuable, and may have implications for other vascular disorders of the central nervous system. This report is the first description of intraoperative monitoring for hyperperfusion states after AVM resection using the intravenous ^{133}Xe method. This CBF technique is becoming more common with numerous studies appearing using similar methodology (10–13).

In this series, obliteration of shunt flow through the AVM increased cortical perfusion bilaterally. The intraoperative CBF values before excision of the AVMs were appropriate for the degree of hypocarbia under isoflurane/nitrous oxide anesthesia. Normal awake CBF in 12 young normal controls, age 26 ± 2 yr, in our laboratory was 63 ± 8 ml·100 g^{-1}·min^{-1} at an end-tidal Paco$_2$ of 45 ± 3 mmHg (14). Assuming a cerebrovascular reactivity to Paco$_2$ of approximately 3% per mmHg in awake normal patients, one could extrapolate to a comparable awake CBF at a Paco$_2$ of 25 mm Hg to 30 ml·100 g^{-1}·min^{-1}. However, flows after excision in the two patients developing complications were considerably higher than would be expected for the intraoperative conditions. The trend for a small increase in temperature in the group as a whole probably contributed to a slight overestimation of CBF values comparing pre- to postexcision CBF values. Temperature raises CBF approximately 5%/°C using similar methodology (13). Similarly, case 4 had a higher Paco$_2$ and an inspired isoflurane concentration during the POST measurement. It was not possible to maintain isoflurane concentration at 0.75% in all patients, but the impact of changes in isoflurane concentration in the 0.75% to 1.25% range should be minimal (15–18). Despite these minor differences, removal of an AVM clearly increases CBF.

AVMs, in general, have an intravascular resistance to flow lower than that of surrounding brain vasculature (19), resulting in a high-flow/low-resistance system. Although the pathophysiology is not clear, it seems likely that autoregulation is abnormal in surrounding tissue. This may well affect tissue perfusion distant from the AVM, extending to the contralateral hemisphere (2). Several lines of evidence implicate significant preoperative steal as an important pathophysiological condition (20). There are numerous reports of neurological deficits that resolved with obliteration of AVM shunt flow by surgery or embolization (21). However, hyperemia and subsequent hemorrhage in relatively normal brain is a major source of postoperative morbidity and mortality following AVM resection (1). A commonly invoked hypothesis suggests that decreased perfusion in the surrounding normal brain sharing the same circulation leads to a state of vasomotor paralysis and that, after resection, blood from the AVM vascular bed is routed into tissue that is unable to autoregulate effectively, resulting in hyperemia or intracerebral hemorrhage. This was termed "normal perfusion pressure breakthrough" by Spetzler et al. (3).

The theory that hyperperfusion injury is operative in complications arising after AVM resection has considerable indirect support from multiple investigations of cerebral hemodynamics, employing a broad spectrum of monitoring techniques (19–28). A similar mechanism has been proposed to be operative after carotid endarterectomy to explain the occurrence of postoperative cerebral hemorrhage (10,29). The higher CBF in patients who went on to develop complications was only a relative increase, and in absolute terms would not be expected to cause damage. Although not measured in this study, it is likely that in these patients, CBF in the awake state was also relatively elevated. This has never been systemically studied postoperatively in AVM patients, but global hyperperfusion has been observed in the postendarterectomy patient (10). Flow elevations corresponding with symptoms of hyperperfusion have been demonstrated by Schroeder et al. after carotid endarterectomy (30).

We have demonstrated elevated blood flow in relatively normal brain parenchyma both near and distant from the AVM following its resection. Two of 11 patients had dramatic flow increases after the AVM removal with development of symptoms of perfusion pressure breakthrough. Intraoperative monitoring of CBF appears to be of use as a means of identifying patients at high risk for development of postoperative complications attributable to hyperperfusion states and to determine optimal perioperative management strategies, especially with respect to arterial blood pressure control. Further testing of cerebral hemodynamics during AVM resection on a large series of patients using the CBF methodology reported in this paper is necessary to confirm this hypothesis.

The authors wish to thank Kenneth Josoewitz, BA, Angela Wang, and Ayelet Barkai for expert technical assistance, Octavio Morales, BS, and Clarence Williams, BA, for computer assistance, TST Wang, PhD, and Philip Alderson, MD, for assistance with radiopharmaceuticals, and Edward D. Miller, Jr., MD, Richard S. Matteo, MD, W. Jost Michelsen, MD, Alexander Brawanski, MD, and Karin Muraszko, MD, for helpful suggestions.

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Letters to the Editor

Lid or Lash Reflex?

To the Editor:

Once again the lid reflex has been defined as a reaction to the stroking of the eyelashes resulting in movement of the eyelid (1). Historically, the eyelid (lid) reflex is elicited by gently raising the palpebra superior. This will cause an increased tone of the musculus orbicularis oculi conductive to closure of the eye. The loss of this reflex was associated with entrance into Stage III of ether anesthesia (2). Reflex motion of the eyelid to stroking of the eyelash was called the eyelash (lash) reflex by Guedel (2).

Inconsistency as to the definition of lid reflex persists in the English language; the eyelash (1) as well as even the corneal reflex (3) have been defined as "lid reflex." As all three different stimuli result in the same eyelid reflex movement, it is appropriate to maintain the historical definitions of these reflexes with regard to type and site of stimulation. Although the clinical significance of all three reflexes during thiopental anesthesia may be the same (1), this may not hold true for all modern anesthetic techniques. The clinical significance is not the same under ether anesthesia: increasing depth of ether anesthesia was noted by Guedel (2) to be associated with depression of these reflexes in the order of eyelash < eyelid < corneal reflex (2).

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Mobile Anxiolysis for Pediatric Ambulatory Surgery Patients

To the Editor:

With increasing emphasis on ambulatory surgery, the search for the ideal preoperative regimen is intensified. Methods used should be pleasant to take, effective, nontoxic, free from side effects, rapid in onset, and short in duration.

We wish to describe a previously unreported method that has had a high degree of success in calming our pediatric outpatients while avoiding prolonged sedation and other undesirable effects often seen with pharmacologic premedication.

A bright red wagon with stake sides (Radio Flyer Town and Country) is kept in our ambulatory surgery unit, creating an object of immediate interest to pediatric patients, with most demanding a ride in the wagon. The few patients that don't ask for a ride will accept an invitation to take one.

The children are also offered a large stuffed bear to ride with them in the wagon to the operating room (Fig. 1). The bear can later be used as a prop to demonstrate to the child the induction of anesthesia. The child is more willing to take a ride into the operating room in the safe confines of this wagon accompanied by a friendly bear. Inhalation induction of general anesthesia can easily be carried out with the child remaining in the wagon by placing a pillow to support the back and head while the patient remains seated. The anesthetist can sit on a chair behind the patient and comfortably introduce the mask while the child focuses attention on the stuffed bear (Fig. 2).

Our experience shows a calm, relaxed, cooperative pediatric patient can be easily achieved without pharmaco-

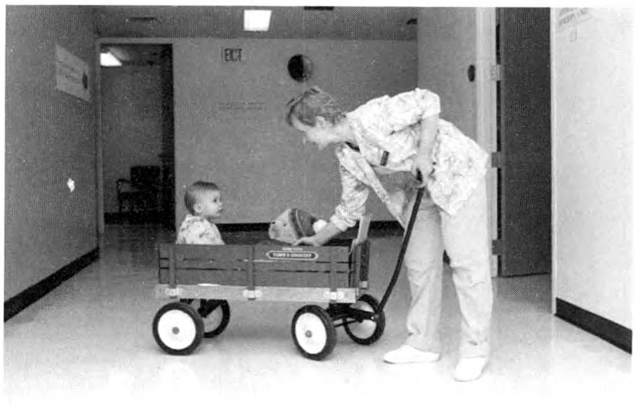

Figure 1. Transport is tailored for the pediatric patient's acceptance.

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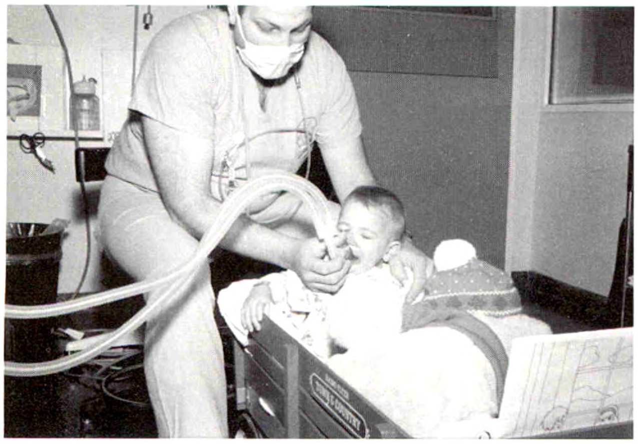

Figure 2. Inhalation induction of anesthesia carried out on a child in the wagon.

logic assistance even in the rapid turnover of a busy ambulatory surgery unit. The wagons are small and take up about one-third the space of a crib or stretcher, which allows their use even when storage space is at a premium. No restraints have been found necessary, and there have been no side effects other than requests to take the wagon home. Siblings of recipients of this anxiolytic therapy have clamored for the therapy when confronted with the need for ambulatory surgery, and parents have not reported any aversion to similar vehicles at home.

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Use of the Fogarty Embolectomy Catheter to Change a Pediatric Endotracheal Tube

To the Editor:

We recently encountered a challenging case involving the need to change an endotracheal tube (ETT) to a smaller size in a child with a potentially difficult airway. We discovered another device to assist in changing ETTs.

A 7-year-old boy presented at an outside hospital with symptoms consistent with croup. Two hours later he developed airway obstruction and was traumatically intubated with a 7.0-mm cuffed ETT. He was transferred to our institution, where the need for direct laryngoscopy and a controlled ETT change was recognized. He was taken to the operating room where anesthesia was induced with halothane and oxygen via the existing ETT. The epiglottis appeared slightly erythematous; all other upper laryngeal structures appeared normal. With the patient spontaneously breathing, a lubricated 7F Fogarty Embolectomy Catheter (FEC) with the Luer Lock adapter removed was passed through the 7.0-mm ETT. The large ETT was removed over the FEC, and a 4.5 ETT was easily placed into the trachea over the FEC guide. The FEC was then removed. The patient did well and was extubated 48 hours later without further airway problems. A urine latex agglutination was positive for Hemophilus influenza.

Several methods have been described for changing ETTs. In adults, the flexible fiberoptic bronchoscope can be useful, but the sizes of our patient's airway and the ETT prohibited use of a fiberoptic bronchoscope (1,2). Various devices have served as "guide wires" for changing ETTs, including suction catheters, urethral catheters, and flexible tipped stylets. Our need for a guide long enough, narrow enough, and yet rigid enough to use with both an adult ETT and pediatric ETT, caused us to look through the operating room supplies and to discover the FEC as a solution.

The FEC has a soft tip to make perforation of the trachea or bronchi unlikely. It has sufficient length to allow its use with most sizes of ETTs, and it has marks along the side to allow easy discernment of depth of insertion. We removed the Luer Lock adapter to facilitate its smooth insertion, but this posed no problems. With sterilization, it could be used again, mitigating the cost of a FEC. The FEC has been used transtracheally to facilitate nonvisualized nasal endotracheal intubation (3). We add changing ETTs to the growing list of uses for the FEC.

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Postanesthesia Recovery Scores and Postoperative Hypoxemia

To the Editor:

The correlation between postanesthetic recovery (PAR) scores and incidence of postoperative hypoxemia reported by Soliman et al. (1) is indeed a genuine attempt to determine if PAR scores may assist on the diagnosis of arterial blood desaturation.

However, their criteria for considering high scores and for discharge of patients from the recovery room deviated from those initially described by Aldrete and Kroulik (2). In our original publication, we considered "high total scores" 8, 9, and 10 and, only when a score of 10 was attained, did we feel that patients were suitable for discharge. The authors (1) included as high scores 7–10 and acceptable scores for discharge 9 and 10. Therefore, it is not surprising that they found a good number of patients with $Sao_2 <$ 95%: if they had followed our original criteria, the number of patients with $Sao_2 <$ 95% would probably have been found to be lower among patients with high scores 8–10 and very few, if any, in patients with total PAR scores of 10.

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2. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg 1970;49:924–33.

In Response:

We thank Dr. Aldrete for his interest in our study showing lack of correlation between PAR scores and oxygen saturation in children recovering from general anesthesia (1).

Dr. Aldrete is correct in noting that our criteria for considering recovery scores to be high and for discharge of patients are different from his original description (2). In our Methods section (and Table 1) we referred to the *modified* Aldrete's scoring system in which the signs of recovery were rewritten to allow easier interpretation in children (1). Like Dr. Aldrete, we believe that children should achieve an overall score of 10 to meet discharge criteria. However, a score of 9 is acceptable if the subtracted point is due to elevated blood pressure, a common finding in children crying after surgery (1).

We re-examined our data using Dr. Aldrete's definition of high scores (8–10). There was still no difference in the proportion of $Sao_2 <$ 95% and $\geq$ 95% among patients who achieved low ($\leq$ 7) or high (8–10) PAR scores in all age groups.

Finally, as we stated in our paper, the 12 patients who still had oxygen saturation < 95% when they were ready for discharge had indeed all achieved a recovery score of 10 at that time. The presence of a resolving upper respiratory infection is one of the possible explanations for that finding (3).

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Postoperative Oxygen Saturation in Children

To the Editor:

Kataria et al. (1) have demonstrated convincingly that infants and children can become significantly hypoxemic during transport in the immediate postanesthetic period. Their data suggest that the younger the patient is, the greater the risk of hypoxemia. I would like to draw attention to a similar study (not mentioned in the above article) done in Detroit (2) Children Hospital, where an equally significant incidence of hypoxemia during transport was reported. In this study two factors had the greatest influence on oxygen desaturation during transport: 1) Minor coughing or light snoring during transport and, 2) the presence of a coexisting condition such as lower airway disease or obesity. The age of the patient had no significant influence on oxygen saturation in this series of 101 cases. I understand from the Kataria article (1) patients who were coughing were carefully excluded from the study. But, I would like to point out that non-smooth transport still happens to be the commonest cause of oxygen desaturation during transport.

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Alkalinized Bupivacaine in Brachial Plexus Blocks

To the Editor:

We read with interest the article by Bedder et al. (1) They found alkalinized bupivacaine without epinephrine (pH 7.05–7.15) was not better in brachial blocks than a stock solution of bupivacaine without epinephrine (pH 5.5). This is in contrast to Hilgier's study (2) of brachial plexus blocks where alkalinized bupivacaine significantly shortened onset time and prolonged duration of action. Bedder et al. (1) point out that Hilgier's study used bupivacaine with epinephrine, which has an initially lower pH (3.9) than bupivacaine without epinephrine (pH 5.5) so that there was a proportionally greater change in pH that may have accounted for the difference in results. However, it should also be noted that Hilgier (2) used 2 mg/kg, whereas Bedder et al. (1) employed 3 mg/kg bupivacaine, 33% more than used by Hilgier. This increase in the amount of drug used by Bedder et al. well may have been why the beneficial effects of alkalinization seen by Hilgier with lower dosages was not observed by Bedder et al. Though Bedder et al. (1) encountered no signs or symptoms of toxicity, the cardiotoxicity of bupivacaine at such high doses has been documented (3). The ability to use lower doses of bupivacaine and still achieve rapid onset of sensory analgesia and longer duration of action with the alkalinized bupivacaine as shown by Hilgier, appears to be more appropriate than the use of larger volumes and higher doses of nonalkalinized bupivacaine used by Bedder et al.

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In Response:

We thank Drs. Parnass and Ivankovich for their interest in our report on alkalinized bupivacaine in brachial plexus blocks (1). Their comments reinforce the importance of comparing local anesthetics with similar physiochemical properties to draw meaningful conclusions. Alkalinization of epinephrine containing 0.5% bupivacaine solutions may be beneficial as demonstrated by Hilgier's (2) work, while alkalinization of plain 0.5% bupivacaine solutions confers no advantage, as shown in our study. We feel this difference is probably related to the proportionally greater change in pH in epinephrine containing preparations as shown in Hilgier's results. It is possible that our larger dose and volume of bupivacaine shortened onset time in both of our groups compared to Hilgier's patients. However, we found no additional effect of alkalinizing the drug we used.

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Folinic Acid Prevents Megaloblastic Changes Associated with Nitrous Oxide

To the Editor:

The letter by Berger et al. (1) is of interest and raises a number of issues regarding the safety of nitrous oxide in terms of bone marrow depression in compromized patients.

An anesthetic lasting 2 hours 15 minutes hardly constitutes a brief exposure, even in a healthy individual. It is certainly not brief in a patient who, before surgery, has hematological signs plus a history of malabsorbtion and vitamin B12 deficiency (1). This is particularly so in view of the finding that as little as 1-hour exposure to the N_2O could cause megaloblastic anemia in a seriously ill patient (2). Recently it has been shown that methionine synthase is inactivated at a much slower rate in humans than in rats and that exposures of up to 45 minutes are unlikely to produce clinically significant effects (3,4). Thus it would appear that exposures in excess of 45 minutes require suitable prophylactic measures in compromized patients. Such prophylaxis is relatively simple, because administration of folinic acid in adequate doses prevents the development of megaloblastic changes (5) even in a severely ill patient who has been exposed to N_2O on two occasions within 24 hours for a total of 3 hours, 45 minutes (6). These preventive measures are of course unnecessary in uncompromized healthy patients in whom exposures of up to 5 hours do not appear to have any clinically significant effects (5). It appears, therefore, provided the correct preventative measures are adopted exposure to nitrous oxide (brief or otherwise) is in order even in patients showing signs of vitamin B12 deficiency and malabsorbtion. In any event, even where such prophylactic measures are not used and signs of myelosuppression develop, postoperative vitamin B12 supplements effectively ameliorate the situation as is well illustrated by this case (1).

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In Defense of the Wake-Up Test

To the Editor:

We read the report of postoperative quadriplegia after spinal fusion for scoliosis with intraoperative awakening by Diaz and Lockhart (1) with interest and found the discussion very informative. However, we beg to differ with their final conclusion that this case represents the "first known false-negative wake-up test."

This case involved a 16-year-old 50-kg male with a 3-year history of what was thought to be progressive idiopathic scoliosis scheduled for an elective posterior spinal fusion with Harrington instrumentation between T5 and L1. Preoperative history included transient neurologic problems of unknown etiology. Anesthesia and surgery were uneventful. The wake-up test was successfully completed with the patient rapidly withdrawing his extremities in response to pinpricks and appropriately moving his feet in response to verbal commands. At the conclusion of the case, the patient was admitted to the recovery room spontaneously moving both lower extremities. Over the next 10 hours the patient developed fluctuating levels of paraplegia from T6 to T8. After several diagnostic and surgical procedures, including reduction of the distraction, the patient was left with T3 flaccid quadriplegia and a diagnosis of syringomyelia (1).

Diaz and Lockhart (1) include a review of the usefulness and limitations of the wake-up test and somatosensory evoked potentials, and briefly mention some of the increased risks of neurologic damage associated with syringomyelia. They then conclude that an intraoperative wake-up may not always prove an absence of neurologic damage during scoliosis repair and assert that the case in point represents "the first known false-negative wake-up test" (1).

It is our feeling that this conclusion is misleading inasmuch as the wake-up test was appropriately negative as demonstrated by the fact that the patient had normal neurologic function in the recovery room and that the quadriplegia did not develop for another 5 hours. In addition, the signs of paraplegia that developed were consistent with a T3 lesion, whereas the intraoperative instrumentation extended only to T5 (1). What is important to note is that although the negative wake-up test demonstrated the absence of intraoperative damage to the spinal cord, it did not predict the development of the subsequent neurologic damage.

As such, we believe that a more meaningful conclusion to this case presentation would be that although a negative wake-up test may demonstrate the absence of intraoperative damage to the spinal cord, this does not guarantee that subsequent neurologic damage may not develop.

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Ephedrine for Treatment of Penile Erection during Spinal Anesthesia

To the Editor:

A 59-year-old, 64-kg male patient with a prostatic hypertrophy was scheduled for a transurethral resection of the prostate. Spinal anesthesia was performed using 12.5 mg of 0.5% tetracaine in 10% dextrose and a sensory level of T6 was achieved. About 30 minutes after surgery was started, penile erection occurred, making continuation of the procedure difficult. Ten mg of ephedrine was then administered intravenously, and within 5 minutes the erection disappeared. Five minutes after the first administration of ephedrine, an additional dose of 10 mg was injected intravenously and thereafter 20 mg of ephedrine was given intravenously over 30 minutes. The surgery was completed without any further recurrence.

It is generally believed that psychic or local sensor stimulation increases a sacral (S2–4) parasympathetic outflow, leading to relaxation of the corpora arterioles and partial closure of the venules and arteriovenous shunt, with subsequent engorgement of the corpora cavernosa. The resulting erection normally subsides after sympathetically mediated arteriolar constriction with a reduction of the blood inflow and an enhanced venous drainage (1). If this is true, a sympathomimetic drug should be effective in relieving an erection. Indeed, direct acting vasoconstrictors such as methoxamine and phenylephrine have been recommended for this purpose (2). Ephedrine may decrease the inflow of the blood to the corpora cavernosa by stimulating the sympathetic nervous system or by a direct-acting effect.

Ketamine has been reported as useful in the treatment of erection during general anesthesia (3–5), but has been found useful during spinal anesthesia (6,7). Nitroglycerin, on the other hand, has been used successfully for treatment of penile turgescence during spinal anesthesia (8). In our case nitroglycerin was not the first choice. Because systolic blood pressure was 110 mm Hg and we wished to avoid a further decrease in pressure.

Although further clinical investigation is needed, if the blood pressure is not elivated, and it rarely is during spinal anesthesia, ephedrine may be useful in the treatment of anerection during spinal anesthesia or even during general anesthesia.

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Cessation of Blood Flow in Intravenous Regional Anesthesia

To the Editor:

Intravenous regional anesthesia is a common and valuable technique providing excellent operating conditions for upper extremity surgery. We wish to describe a method of accurately determining the blood pressure at which arterial flow ceases in the extremity. This provides assurance that pressures in the tourniquet are sufficiently high to prevent arterial blood from entering the extremity, while at the same time preventing escape of local anesthetic solution into the peripheral circulation.

Two methods for determining proper tourniquet pressures seem to be most popular (1) the absence of Doppler tones over the radial artery, or setting an arbitrary tourniquet pressure (i.e., 300 mm Hg). Of these methods, we have used the absence of Doppler tones as an indicator of arterial occlusion. A Doppler ultrasound flow probe (Parks Medical Electronics; Beaverton, Oregon) is placed over the ipsilateral artery. Controlling the tourniquet pressure while holding the probe motionless over the artery is often awkward. The Doppler device also produces extraneous background noise which is irritating to the patient and other personnel in the operating room.

Pulse oximeters (Ohmeda Corporation) are present at each anesthetizing location in our hospital. We, and others (2), have noted that the oximeter alarm system is extremely sensitive to cessation of arterial blood flow. The multi-use "clothespin" probe is placed over a digit on the extremity. Once an adequate tracing is obtained, the tourniquet pressure is incrementally increased until digital blood flow has ceased. The tourniquet pressure is then set 50 to 100 mm Hg higher, the probe is moved to the opposite extremity, and the block is started.

This method allows the anesthesia provider to manipulate tourniquet pressures and assess the integrity of the double-cuff system with a minimum of clumsiness. Using the oximeter probe as a measure of arterial flow is simple, sensitive, and appears to be as accurate as the Doppler flow probe (unpublished data).

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Pitting Edema and Intravenous Access

To the Editor:

I wish to describe a simple technique to aid in placement of intravenous cannulae in patients with peripheral edema. This is a common problem in intensive care units and in obstetric patients with pregnancy-induced hypertension, and may be compounded by extravascation of previous intravenous infusions and unsuccessful attempts at cannula placement.

Edema is caused by an excess of interstitial fluid. Subcutaneous edema causes swelling that obscures subcutaneous veins, thus making successful venipuncture very difficult. This subcutaneous edema will "pit" on pressure, i.e., digital pressure displaces fluid from the tissue compressed and leaves a depression in the swelling, which slowly fills in as interstitial fluid gradually moves back into the area, once the pressure has been released. This is a familiar clinical sign in clinical medicine.

Pitting edema can be used in the placement of an intravenous cannula. If the dorsum of a patient's hand is compressed manually for one minute, the edematous fluid will be temporarily displaced and the underlying veins become visible and accessible. These veins are usually in good condition because they have been shielded by the overlying edema. Cannulation is then usually easy.

In 5 years of clinical practice, I have had reason to use this technique on at least 30 occasions. It was unsuccessful on only two occasions and in one of these the difficulty in cannula placement was compounded by marked obesity. On six other occasions, when the technique has been suggested by me, colleagues have been successful and have been impressed by the ease with which venous access was achieved. Though my experience with the technique has been limited to cannula placement in the upper limbs, I see no reason why it should not be applied to the lower limbs. This simple technique will on occasion obviate the need to place a central venous catheter merely to assure venous access.

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Book Reviews

Neural Blockade in Clinical Anesthesia and Management of Pain, Second Edition

Michael J. Cousins, Phillip O. Bridenbaugh, eds.
Philadelphia: Lippincott, 1987, 1171 pp, $149.50.

The classic novel withstands changes in history because the author has found a theme and has expressed it in a manner that subsequent generations can appreciate. A textbook, on the other hand, only remains a classic when its authors are able to use changes in history to their advantage. Cousins and Bridenbaugh, published their first edition of *Neural Blockade in Clinical Anesthesia and Management of Pain* in 1980. Though only eight years have passed, a new, second edition has been published because so much has changed that the original had become inadequate.

Unlike the novel, the textbook adapts. The author's style, presentation and subject matter can always be modified. These two editors have brought together 41 contributors (including many new ones) from 10 countries. The authors, experts in their own right, have published extensively in many diversified areas. Their styles differ, but this is a major advantage for delivering the amount of material in this textbook.

The table of contents has been modified so that major topics such as Techniques of Neural Blockade can easily be divided into specific areas. Type and format eases the reader's worries about finding the appropriate chapter. There has been some restructuring of chapters, and the manner in which content is presented is a significant and worthwhile change.

Subject material is presented simultaneously in several chapters, and the reader is assurred that material that might be missed or misunderstood will reappear. Obviously, the index is extremely important and this reviewer used it extensively. For the one who prefers a "one shot" approach to a subject, that reader would find the editors disagree with that technique and rely on their authors to present the information in as many ways as possible. Some authors have been assigned to write the same chapter in both editions and have made slight changes. Fortunately, many chapters have been rewritten by new authors. Extensive revision and expansion on the subject of chronic pain was achieved through 11 new chapters and one from the first edition. This is an important topic in the multidiscipline areas represented by anesthesiology, neurology, psychiatry, neurosurgery and medicine; the editors have covered the field well.

Practicing anesthesiologists, residents, and teachers will find the figures, tables, anatomic illustrations and freehand drawings more than adequate to supplement the written word. Multiple needle locations on colored anatomic representations are useful and easy to refer to during practice. One wishes, however, that a separate cross-referenced index were present for quick access to these illustrated techniques.

Cousins and Bridenbaugh have been successful in their attempt to provide a thorough and complete textbook on the subject of pain. This work is a necessity for the personal and departmental library of those who specialize in pain management.

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New Anesthetic Drugs (Anesthesiology Clinics of North America)

R. J. Fragen, ed. Philadelphia: WB Saunders, 1988, 210 pp, $27.00.

The role of such hardcover serial monographs is to provide the reader with concise, clinically applicable material. This information is often more up-to-date than that found in textbooks and reasonably well-referenced. The current issue of the *Clinics* fulfills such a role. The authors have succeeded for the most part in integrating their discussions of new compounds and those already in use. The only exception appears to be the somewhat weak discussion of obstetrical drugs. Except for the sections on uterine active agents and regional anesthesia, much of the material is discussed in more depth elsewhere in the book.

The chapter on pharmacokinetics and pharmacodynamics is more difficult to read than the others. Nonetheless, the authors have done justice to many of the concepts. Particularly noteworthy are those of potency and efficacy, which are more clearly discussed here than in the pharmacology text from which the diagrams were obtained.

One might argue that the section covering inhaled anesthetics is misnamed, because only a brief portion was

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devoted to the new agent sevoflurane. The authors, however, have managed to provide the reader with a keen insight into the timely cardiac and neurological considerations with respect to isoflurane.

The only section confined to new drugs alone was the discussion of cardiac medications. This was the longest chapter (35 pages) and had the most references (170)—yet it focused on only three drugs. Nevertheless, these drugs (two beta blockers and one inotrope) have had a profound influence on recent anesthetic practice.

The topic with the fewest citations (10) was that of intravenous drugs. Oddly enough, there are no references pertaining to Ketamine. This is especially suprising in light of the author's prior extensive review article on the same drug. In addition, one might take issue with some potentially misleading statements, such as the description of respiratory stimulation by Ketamine. The latter impression resulted from comparisons of CO_2 responses in dogs receiving Ketamine with historical controls of other investigators. Bourke, et al. (Anesthesiology 66:153, 1987) have clearly shown that Ketamine produces respiratory depression in humans qualitatively similar to premedicant doses (0.2 mg/kg) of morphine. Another statement in the otherwise excellent chapter concerns the explanation of decreased thiopental requirements in the elderly. The author quite reasonably attributes these to a smaller volume of distribution, i.e., a pharmacokinetic change. The authors of the pharmacokinetic section provide a more in depth discussion of this topic and actually hedge their bet by offering the suggestion that the age-related differences in thiopental sensitivity may be due to pharmacodynamic changes not detectable with techniques currently available. The lack of even a mention of benzodiazepene antagonist such as flumazenid in the chapter on psychotropic drugs is a surprising omission. Perhaps this reflects the uncertainty regarding this drugs action in humans.

This contribution to the series is a reasonable one and worth considering as a single item despite the sizeable price tag.

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Perspective in Shock Research

R. F. Bond, H. R. Adams, J. H. Chandry. New York:
Alan R. Liss, 1988, 452 pp, $90.00.

This volume (No. 264) from a series entitled "Progress in Clinical and Biological Research," is a compilation of the proceedings from the Tenth Annual Conference on Shock and First International Shock Congress held in Montreal, June 7–11, 1987. The focus of the conference was on hypotension and tissue hypoperfusion, with a balance of basic research and clinical studies. The wide range of international participants is well represented in these articles and selected papers, which include transcripts of 4 symposia (19 articles), 2 workshops (11 articles) and selected abstracts of poster and slide presentations (20 of the 199 actually presented).

The first symposium reviews mechanisms of cell injury in a variety of models of shock, sepsis, and burn injury. The hypothesis is presented that the mechanisms of injury are similar despite the apparent difference between low flow states (hypotension or arterial occlusion) and high flow states (burns, sepsis). The phenomena supporting the "calcium overload" hypothesis and the "oxygen surplus" hypothesis are discussed in relation to reperfusion injury and to metabolic responses to burns, trauma, and sepsis. Some of the biologic mechanisms which may protect organs from damage are examined; specific differences between organs may explain differences in sensitivity, e.g., brain, heart, kidney, and liver. The liver enjoys the most attention in this series of articles, because, in combination with poor blood flow autoregulation and high metabolic demands during shock, activation of the reticuloendothelial system (Kupfer cells) induces major changes in metabolism of hepatic parenchymal cells, little of which is understood. The same kind of altered metabolism and cell damage may also be induced in other tissues by the circulating products of the activated macrophage.

The next symposium is an excellent review of the animal studies, human observations, and statistical analysis that were used in the design and conduct of the Veterans Administration Cooperative Study, Number 209, "Evaluation of Corticosteroid Therapy in Severe Sepsis." The peculiar problems of studying this group of patients are presented, not the least of which is the problem of informed consent in a population whose selection may be based on mental status deterioration. The outcome of this study was that steroids made no difference in overall survival; the study was successful by a number of criteria, but failed to answer questions about important subgroups of patients. The papers in this symposium are thus a valuable reference for any investigator who is contemplating clinical trials.

A third symposium reviews the role that humoral mediators serve in shock, including vasoconstrictor (angiotensin II is responsible for lesions of the GI tract after trauma, sepsis, and cardiopulmonary bypass), eicosanoids (thromboxane and leukotrienes appear to fulfill criteria as mediators of damage in ischemia and shock), and monokines (TNF, interleukins, interferons, platelet-derived factors, and complement). The prognostic significance of circulating endotoxin is explored in two articles.

The symposium entitled, "Central Nervous System" includes an article on the cerebral circulation in shock, as well as two articles describing impaired reflex control of cardiovascular functions caused by hypoperfusion of the CNS; another article explores the pharmacologic basis for preventing hypoxic or ischemic CNS damage. An article describing experimental nonpenetrating head injury seems out of place here.

Two workshops follow, the first describing the features of septic shock in the very young and the elderly, whose response to injury or infection is impaired. The second covers mechanisms and approaches to therapy; a wide range of topics is covered, including the role of the endogenous opiates in shock and the use of naloxone, glucagon, and TRH in treatment. Two articles discuss the difficulties of the single-mechanism, single-treatment approach to shock.

Finally, a number of research papers selected on the basis of "quality and timeliness" are reproduced. Some of these correspond to topics that appear elsewhere in the book; others deal with subjects not covered at all, such as ARDS and right ventricular failure in sepsis.

As with many reports of meetings, journal publications outrace the book publisher (and the reviewer). For instance, the articles on the VA Cooperative Study now serve best as accompaniment to the definitive scientific reports, illuminating some of the decision processes in the design and execution of the study. A large part of the work reported here is available in more complete form elsewhere, and some has been superseded.

The one striking flaw in this collection of papers is the almost total absence of discussion of pulmonary dysfunction in sepsis. To quote one paper, "usually the respiratory distress syndrome is present in some form during hypermetabolism," but nowhere are the etiology, consequence, prevention, or treatment of ARDS discussed. The major emphasis is on the gastrointestinal tract as the primary source of agents of organ injury. However, the biochemical factors described in these papers also have profound influence on pulmonary metabolism and gas exchange, on which the rest of the organism depends.

Unfortunately, the publisher has reproduced the articles as received from the authors. The result is a gamut of styles that diminishes the quality of the publication. For instance, in one article on cellular aspects of shock, the typeface, single spacing, and primitive justification combine to produce unreadable text. There are other examples that, although not illegible, are difficult to read. Many typographic errors occur in the text; several paragraphs are uninterpretable (undoubtedly the result of superficial editing).

For the critical care clinician or shock researcher, this book is a modest sampler of review, recent research, and clinical application. The articles on the VA Cooperative Study are excellent examples of the process of design and execution of a clinical study and of the statistical analysis of patient data. For the merely interested, the content of this book is too uneven to justify its price.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal. The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Coetzee A, van der Merwe W (eds): An Introduction to Anaesthesiology, Oxford Univ Press, New York, 1988. 520 pp.

Ellison N, Jobes DR (eds): Effective Hemostasis in Cardiac Surgery, WB Saunders, Philadelphia, 1988. 209 pp, $75.00.

Regnier B, Brun-Buisson C: L'Infection/en/Reanimation, Masson, Paris, 1988. 288 pp, $43.20.

Renck H (ed): Bleeding and Thrombotic Disorders in the Surgical Patient, Appleton & Lange, East Norwalk, Ct, 1988. 177 pp, $35.00.

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2. *Personal author(s) books and monographs*
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3. *Chapter in a book*
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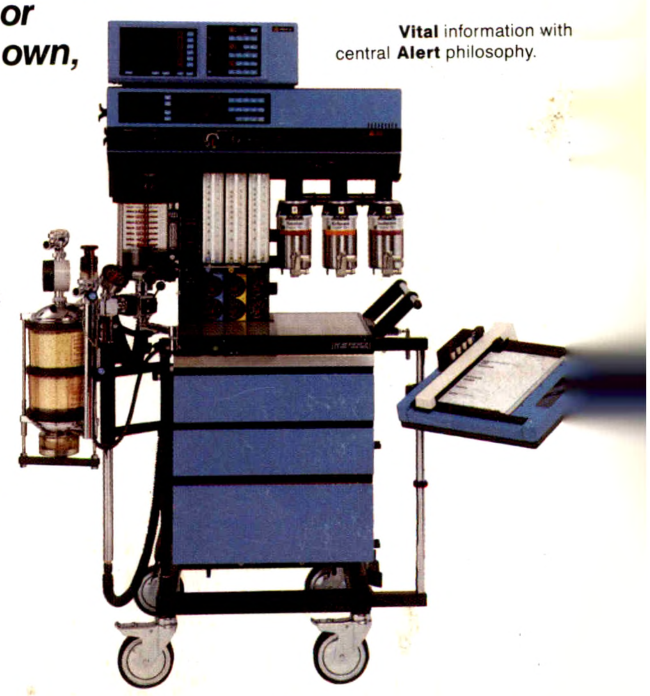

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